FORMULATION DEVELOPMENT OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS

Dissertation submitted to
The Tamil Nadu Dr. M.G.R. Medical University, Chennai
In partial fulfillment of the requirements for the award of the Degree of

Master of Pharmacy
IN
Pharmaceutics
April – 2012

Under the guidance of

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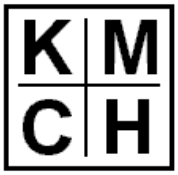

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DECLARATION

I am here by stating that, to the best of my knowledge and belief, the project report entitled ***"Formulation Development Of Metformin Hydrochloride Sustained Release Tablets"*** *being submitted for the partial fulfillment of* ***Master of Pharmacy*** *in* ***Pharmaceutics*** *for the academic year 2011-2012 of KMCH College of Pharmacy affiliated to The Tamilnadu Dr.M.G.R. Medical University carried out under the guidance of* ***Dr. K.S.G. Arul Kumaran, M.Pharm., Ph.D.,*** *Head, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore.*

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EVALUATION CERTIFICATE

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ACKNOWLEDGEMENT

I submit my sincere thanks and respectful regard to our beloved Managing Trustee **Dr. Nalla G. Palanisamy and Dr. Thavamani D. Palanisamy** for all the faculties that were provided to me at the institution enabling me to do the work of this magnitude.

I take this opportunity with immense pleasure to express my gratitude for the help rendered my dissertation with success.

I would like to express my sincere gratitude to **Dr. K.S.G. Arul Kumaran,** Head of the Department of Pharmaceutics, KMCH College of Pharmacy, for guiding me throughout this project.

I express my sincere thanks and gratitude to **Dr. Rajasekharan** Principal, KMCH College of Pharmacy.

I confer my heartfelt thanks to **Dr. R S Prasad,** R&D Manager, Suven Nishtaa Pvt Ltd, Hyderabad for his valuable guidance and support for my work on this topic.

I wish to express my special thanks to industrial guide **Mr. Kamalakar Rao.** M. Pharm for giving me an opportunity for an exposure to a research and development of project.

I express my sincere thanks to **Dr. Padmakumar Kaimal** (Suven Life and Science) who give me on opportunity to do project in company.

I specially thank to **Mr. Sreenavas,** Head of Pilot Plant, **Mr. Sasi Reddy,** Analytical R&D Manager and analytical department members of Suven Nishtaa Pharma Ltd, Hyderabad.I also express my heart ful thanks to Anand ,Rakesh ,Kamalendra , Sreekanth , Pranith ,and R&D department members for their valuable guidance to finish my project .

My special thanks to **Dr Arun Kumar** for his valuable support.

I owe my deep debt of gratitude to our esteemed and beloved staff, **Mrs. Padmapreetha,** M.Pharm., and **Mr, Shankar,** M.Pharm., and my sincere thanks to all other staff of KMCH College of Pharmacy, Coimbatore who directly or indirectly gave me a helping hand.

This project would not be a resplendent one without the timely help and continuous support by my ever-loving friends of pharmaceutics **(Sreejith, Dineesh, Mazin, Sagar, Christy, Lincy Varghese, Lincy John, Sandra, Ambika, Rekha).**

Above all I declare myself before the unfailing presence of **God** and constant love and encouragement given to me by **beloved parents** and my remaining **family members** who disserves the credit of success in what our work I did.

Mr. Arun Raj

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

API	-	Active pharmaceutical ingredient
IP	-	Indian pharmacopeia
MR	-	Modified Release
HPMC	-	Hydroxypropyl methylcellulose
Ethocel	-	Ethylcellulose
PVP	-	Povidone
C_{max}	-	Peak Plasma Concentration
T_{max}	-	Time for Peak Plasma Concentration
BP	-	British Pharmacopoeia
EP	-	European Pharmacopoeia
JP	-	Japanese Pharmacopoeia
ICH	-	International Conference on Harmonization
LOD	-	Loss on Drying
FDA	-	Food Drug Administration
°C	-	Degree Celsius
NDA	-	New Drug Application
PEG	-	Polyethylene Glycol
HPLC	-	High Performance Liquid Chromatography
UV	-	Ultra Violet
NMT	-	Not More Than
LOQ	-	Limit of quantification
RRT	-	Relative retention time
USP	-	United States Pharmacopoeia
rp	-	reference productrm
RMG	-	Rapid Mixed Granulator
FBD	-	Fludised bed Drier

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration, belief that by oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology,[1] pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

In recent years, scientists[2] have focused their attention on the formulation of sustained release tablets. The task of developing sustained release tablets is accomplished by using a suitable hydrophilic polymer.[3]

1.1. Tablets

1.1.1. General Introduction

What is tablet?

Tablets are solid preparations which contain a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration in which some are swallowed as whole, some are after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. Tablets are usually round, circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled. Tablets may be coated.

The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances are capable of modifying the behavior of the tablet in the digestive tract, colouring matter authorized by the competent authority and flavoring substance.

1.1.2. Type and classes of tablets: -

a. Oral tablets for ingestion

- Compressed tablets
- Multiple compressed tablets
- Layered tablets
- Compression-coated tablets
- Repeat-action tablets
- Delayed-action and enteric- coated tablets
- Sugar and chocolate – coated tablets
- Film coated tablets
- Chewable tablets

b. Tablets used in oral cavity

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

c. Tablets administered by other routes

- Implantation tablets
- Vaginal tablets

d. Tablets used to prepare solutions

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Table t triturates

1.1.3. Tablet can be prepared by the following method[4]

a. Wet granulation

b. Dry granulation (Slugging technique)

c. Direct compression

Ideal characteristics of Table t dosage form

It has its own identity, free of chips, cracks, discoloration and Contamination. It should have strength to withstand mechanical shocks encountered in its production, packaging, shipping and dispensing. It should have chemical and physical stability.

1.1.4 .Comparison of major steps involved in the Tablet manufacturing methods

Table .1

Steps	Wet granulation	Dry granulation	Direct compression
Step 1	Mixing / blending of API and adjuvants	Mixing / blending of API and adjuvants	Mixing / blending of API and adjuvants
Step 2	Preparation of binder solution	Compression in to slugs	Compression
Step 3	Massing of binder solution of step 2 with powder mixture step 1	Size reduction of slugs and sieving	
Step 4	Wet screening of damp masses	Mixing of granules with Pharmaceutical aids	
Step 5	Drying of wet granules	Compression	
Step 6	Resifting of dried granules and blending		
Step 7	Compression		

1.1.5. Different Excipients used in the tablet Formulation[5]

Excipients are inactive ingredients these are added in the formulation to influence the absorption and bioavailability problems and ensure the acceptability, physicochemical stability during the shelf life, uniformity of the composition and dosage. Commonly used Excipients are Diluents (Fillers), binders and granulating agents, disintegrants, lubricants, glidants, emulsifiers. Surfactants, dissolution enhancers, dissolution retardants, buffering agents, lubricants, glidants coating agents, colorings agents, sweetening agents etc.

Diluents (Fillers)

Diluents are commonly added in the formulation (table t and capsules) to produce the necessary bulk. Diluents may be organic or inorganic subatances.among organic

diluents carbohydrates are widely used e.g. starch, lactose, microcrystalline cellulose. The hydrophilic powders are very useful in promoting the dissolution of poorly water soluble drugs e.g.Dicalcium phosphate.

Vehicles

Vehicles or solvent system is major component of liquid oral parental. 3 major categories of vehicles are aqueous vehicle (water, syrup, etc), non aqueous water miscible vehicles (propylene glycol, and sorbitol) and non aqueous water immiscible vehicles (Vegetable oils). Bioavailability of drugs from vehicles depends to a large extent on its miscibility with biological fluids.

Binders

Binders hold the ingredients in a table t together. Binders ensure that tablets and granules can be formed with required mechanical strength, Binders are usually starches, sugars, cellulose or modified cellulose such as microcrystalline cellulose, hydroxypropyl cellulose, lactose, Solution binders are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose and polyethylene glycol.

Disintegrants

Disintegrants expand and dissolve when wet causing the table t to break apart in the digestive tract, releasing the active ingredients for absorption. They ensure that when the table t is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution. Examples of disintegrants include: crosslinked polyvinyl pyrrolidone, sodium starch glycolate, crosslinked sodium carboxymethyl cellulose (crosscarmellose).

Colouring agents

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication.

Glidants

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce

die wall friction. Examples include Colloidal silicon dioxide, talc, and magnesium carbonate.

Lubricants

Lubricants prevent ingredients from clumping together and from sticking to the table t punches or capsule filling machine. Lubricants also ensure that table t formation and ejection can occur with low friction between the solid and die wall.Common minerals like talc or silica, and fats, e.g. vegetable stearin, Magnesium stearate or Stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

Preservatives

Preservatives used to prevent the microbial growth and external factors pharmaceutical formulations are e.g. antioxidants like vitamins, the amino acids (cysteine, methionine)

Sweeteners

Sweeteners are added to make the ingredients more palatable , especially in chewable tablets such as antacid or liquids like cough syrup. Therefore, tooth decay is sometimes associated with cough syrup abuse. Sugar can be used to disguise unpleasant tastes or smells.

Flavours

Flavours can be used to mask unpleasant tasting active ingredients and improve the likelihood that the patient will complete a course of medication. Flavourings may be natural (e.g. fruit extract) or artificial. -a bitter product - mint, cherry or anise may be used.

Coatings

Tablet coatings protect table t ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. For most coated tablets, a hydroxy propylmethylcellulose (HPMC) film coating is used which is free of sugar and potential allergens. Occasionally other coating materials are used, for example synthetic polymers, shellac, corn starch zein or other polysaccharides.

1.1.6. Drug-Excipient Interactions and their Effect on Absorptioion

Excipients[6] are traditionally thought of as inert but they can have a tremendous impact on the pharmacological availability of a drug substance when added to a formulation. The magnitude of this effect will depend on the characteristics of the drug and on the quantity and properties of the Excipients. Excipients have traditionally been classified according to the function they perform in a formulation, although many Excipients perform multiple functions. Diluents allow the formulation of a practically sized tablet and can form large proportion by weight of a formulate product when, for example, the active ingredients is very potent. (The physical characteristic of the diluents are important, for example, triamterene was shown to dissolve more rapidly when it was formulated with hydrophilic fillers such as lactose and starch as compared with insoluble diluents) . Disintegrates tend to swell when wetted and so are added to a formulation to facilitate the breakdown of the dosage form in to granules and powder particles. The newer disintegrates ,called super disintegrates ,cause an extremely rapid break up of a tablet owing their ability to swell to many times their original size .wicking and swelling were found to be the primary mechanism of action for tablet disintegrants,while other mechanisms ,such as deformation recovery , particle repulsion theory, heat of wetting and evolution of gas etc , may play a role in particular cases of tablet disintegration (Kanig and Rudnic ,1984).

Co processing is defined as combining or more established Excipients by an appropriate process .co processing of Excipients could lead to formation of Excipients with superior properties compared with the simple physical mixture of their components or with individual components A large number of co processed diluents are commercially available. The representative examples are Ludipress , Cellactose , and starlac . the use of co processing is a totally unexplored avenue in disintegrants . The widely used super disintegrants are sodium starch glycolate , crospovidone, and croscarmellose sodium.

Wet granulation is a size enlargement process in which a liquid is used to achieve agglomeration of solid particles in a formulation. Agglomeration of solid particles in pharmaceutical formulation improves their properties for tabletting by rendering the particles free flowing , non-segregatting and suitable for compression (Kristensen,1988) . High shear forces in high- speed mixers are widely used in the pharmaceutical industry

for wet granulation.several studies have investigated granulation parameters in high-shear mixers(Shaefer et al ., 1986; Wehrle et al.,1993;Shiraishi et al.,1944) . processing parameters were shown to affect the growth rate of granules in the high-shear wet granulation process.

1.1.7. Different Methods for Table t Preparation

Tablets are manufactured by wet granulation, Dry granulation or direct compression method.

a. Wet Granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablets.

Advantages wet granulation methods

- Suitable for moist and heat sensitive drugs. Robust process suitable for most compounds.
- Imparts flow ability to a formation can reduce the elasticity problems.
- Binding the drug with Excipients thus reducing segregation problem.

Disadvantages of wet granulation methods

- Stability may be major concern for moisture sensitive or thermo labile drugs.
- Any incompatibility between formulation components is aggravated.
- Properties of granules formed may be affected by processing variables like viscosity of granulating solution.
- The rate of addition of granulating solution.
- Type of mixer used and duration of mixing.
- Method and rate of dry and wet blending.

b. Dry Granulation

In this technique, there is no use of liquids. The process involves the formation of slugs. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablets.

Advantages of Dry Granulation process[7]

- The variables faced in the processing of the granules can lead to significant table problems.
- It is suitable for heat sensitive and moisture drugs.
- It is suitable for poor flow drugs. Because particle size of the can be increased.

Disadvantages of Dry Granulation process

- Not suitable for all compounds , Compared to other methods it is a slow process
- Lack of moisture may give rise to static charges, which may lead to segregation .

c. Direct compression

The term direct compression is used to define the process by which tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity & forms a firm compact.

Advantages of direct compression methods

- Reduced processing time, less number of equipments used, less power consumption and labor costs.
- Fewer manufacturing steps and less process validation.
- Elimination of heat and moisture, thus increasing the stability.
- The suitability of the process for thermo labile and moisture sensitive API's.
- The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.
- Provides stability against the effect of aging which affects the dissolution rates.
- Prime particle dissolution.
- In case of directly compressed tablets after disintegration, each primary drug
- Particle is liberated. While in the case of tablets prepared by compression of Granules, small drug particles with a larger surface area adhere together into larger Agglomerates; thus decreasing the surface area available for dissolution.

Disadvantages of direct compression methods

- High dose drugs having high bulk volume, poor compressibility and poor Flow ability is not suitable for direct compression.
- Many active ingredients are not compressible either in crystalline or amorphous

forms.

- The choice of Excipients for direct compression is extremely critical. Direct Compression diluents and binders must possess both good compressibility and good flow ability.
- Problems in the uniform distribution of low dose drugs.
- Direct compression blends may lead to un blending because of difference in particle Size or density of drug and Excipients.
- Lack of moisture may give rise to static charges, which may lead to segregation.
- Capping, lamination, splitting, or layering of tablets due to air entrapment.

1.2. Dissolution

Dissolution is the process by which a solid solute of only fair solubility characteristics enters into the solution (Abodu M et.al, 1989). As a fundamental phenomenon, it is controlled by an affinity between the solid and the medium. Suggested that the dissolution rate is controlled by the rate of diffusion a very thin layer of saturated solution that forms instantaneously around the solid particle.

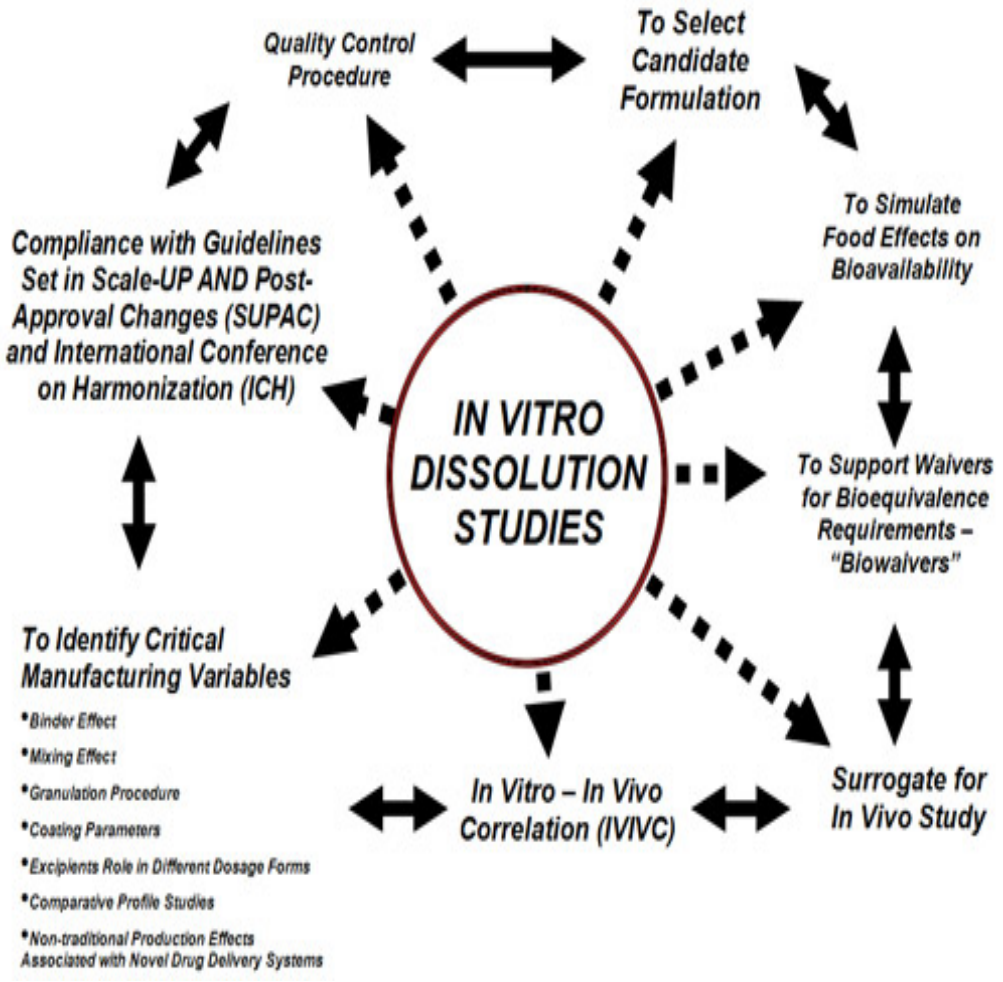
1.2.1. Reasons for tablets dissolution[8]

In vitro dissolution testing of solid dosages form is important for numbers of reasons are

- It guides the formulation and product development toward product optimization. Dissolution studies in the early stages of a product's development allow.
- Differentiation between formulations and correlations identified with in vivo bioavailability data.
- The conduct of such testing from early product development through approval and commercial product ensures control of any variables of materials and process that could affect the dissolution and quality standards.
- It is a requirement for regulatory approval of marketing for product registered with the FDA contains the in vitro dissolution data generally obtained from batches used in pivotal clinical and /or bioavailability studies conducted during product development. Once the specifications are established in an approved NDA, they become official (USP) specifications for all subsequent batches and bioequivalent products.

1.2.2. Application of *In -Vitro* Dissolution Studies

Fig: 1 – Invitro Dissolution Studies



1.2.3 .Factors affecting the Rate of Dissolution Relating to the Solid Dosage Form[9]

a. Effect of formulation factors on table t dissolution rate

The dissolution rate of a pure drug can be altered significantly when mixed with various adjutants during the manufacturing process of solid dosage forms. These adjutants are added to satisfy certain pharmaceutical functions such as diluents, dyes, binders, granulating agents, disintegrants and lubricants.

b. Diluents & Disintegrants

Increasing the starch content (most commonly using diluents from 5 to 20% resulted in a dramatic increase in the dissolution rate of Salicylic acid tablets. This was attributed to better disintegration. Later, Finholt suggested that the hydrophobic drug crystals acquire a surface layer of fine starch particles that imparts a

hydrophilic property to the granular formulation and thereby increase the effective surface area and hence the dissolution rate.

c. Binders & Granulating Agents

Differences in binders used for Tolbutamide tablets resulted in variable dissolution characteristics and differences in the hypoglycemic effect observed clinically. Wet granulation has been shown to improve dissolution rates of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules.

- Magnesium stearate, a hydrophobic - lubricant tends to retard the dissolution rate of Salicylic acid tablets, while a water soluble surface active lubricant, sodium lauryl sulphate, enhanced the dissolution.
- Stearates like Aluminum stearate, Stearic acid and talc decrease the effective drug solvent interfacial area by changing the surface characteristics of the tablets which results in reducing its wet ability, prolonging its disintegration time.
- The enhancing effect of sodium lauryl sulphate, on the other hand, was suggested to be due, in part, to an increase in the microenvironment pH surrounding the sparingly soluble weak acid and to increase wetting and better solvent penetration into the tablets and granules as a result of lowering the interfacial tension between the solid surface and the solvent.

d. Effect of processing factors

The many processing factor used in table t manufacturing greatly influence the dissolution rates of the active ingredients. The method of granulation as well as the compression force used in the letting process, all contributes to the dissolution rate characteristics of the final product.

e. Method of granulation

Granulation process, in general, enhances the dissolution rate of poorly soluble drugs. The use of fillers and diluents, such as starch, spray - dried lactose and Microcrystalline Cellulose, tend to increases the hydrophilicity of the active ingredients and improve their dissolution characteristics. the wet granulation procedure was considered as a superior method compared to the dry double compression procedure. With the advent of newer tabletting machines and materials, it became more evident that the careful formulation and proper mixing sequence and

time of adding the several ingredients are the main criteria that affect the dissolution characteristics of the tablets and not the method or granulation process.

1.2.4. Effects of test parameters on dissolution rate agitation

The relationship between intensity of agitation and the rate of dissolution varies considerably according to the type of agitation used, the degree of laminar and turbulent flow in the system, the shape and design of the stirrer and physico-chemical properties of the lid. When a stirring device is used such as the basket, paddle, rotating filler etc, the speed (or) agitation generates a flow that continuously changes the liquid solid interface between the solvent and the drug in a way similar to the flow rate through dissolution apparatus. In order to prevent turbulence and sustain a reproducing laminar flow, which is essential to obtain reliable results, either the speed of agitation (or) the flow rate, depending on the type of apparatus employed, should be maintained at a relatively low level.

The empirical relationship between the rate of dissolution and the intensity of agitation is

$$K = a\,(N)^{b} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where

N is the speed of agitation, K is the dissolution rate and a & b are constants

Other factors that affect the correlation between agitation and dissolution rate include the density of the solid phase, the size and characteristics of the solid, the stirrer, the dissolution vessel and the of solution of the solute.

a. Temperature

Generally a temperature of 37° C is always maintained during the dissolution determinations. The effect of temperature variation of dissolution medium depends mainly on the temperature solubility curves of the drug and excipients in the formulation for a dissolved molecule. The diffusion co-efficient, D, is dependant upon the temperatures T, according to the stock's equation.

$$D = KT\,(6\pi\, nr) \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where

K is the Boltzmann constant and, 6π nr is the stoke's force for a spherical molecule (n is the viscosity in cgs (or) poise units and, r is the radius of the molecule).

b. Dissolution medium

The selection of proper fluid for dissolution testing depends largely on the solubility of the drug, as well as economy and practical reasons. Various medium used in Dissolutions are pH 1.2, 2.5, 4.5, 6.5, and 7.8

c. Viscosity of the Medium

In the case of diffusion controlled dissolution processes, it would be expected that the dissolution rate decreases with an increases in viscosity. In the case of interfacial controlled dissolution processes however, viscosity should have very little effect. The stokes Einstein equation describes the diffusion co-efficient D, as a function of viscosity. Brawn and Parrott showed that the dissolution rate of Benzoic acid was inversely proportional to the viscosity of the dissolution medium utilizing various concentrations of sucrose and methyl cellulose solutions.

1.3. Modified Release[11]

1.3.1. Definition

Modified release dosage form having the time course and /or location of the drug release chosen to accomplish therapeutic or inconvenience objectives not offered by conventional dosage forms. Various types of Modified release products (mainly oral, but also transdermal, intra muscular, subcutaneous)

1.3.2 .Modified release delivery systems may be divided into three categories

1. Extended release dosage forms
2. Delayed release dosage forms
3. Targeted release dosage forms

1. Extended release dosage forms

The release starts immediately, but is slow, results two fold reduction in dosing frequency Extended release dosage forms further divided in to two types they are

a. Prolonged dosage forms

b. sustained release dosage forms

a. Prolonged dosage forms

Release the drug slowly, provides a drug continuous supply over an extended period.

b. sustained release dosage forms

Delivers an initial (loading) dose immediately, the loading dose is followed by a slow and constant release.

2. Delayed release dosage forms

Releases a discrete portion at later time, although one portion can be released immediately. Delayed release dosage forms further divided in to two types they are

a. Enteric coated tablet

The enteric coating table t is stable in stomach pH; it will dissolve in the higher pH of small intestine.

b. Repeat action tablet

The first dose is released immediately; the second dose is released later saves one administration.

3. Targeted release dosage forms

Releases drug at or near the intended physiologic site of action.

Targeted release dosage forms release the drug by following steps

- **First order targeting**

  Drug is delivered to the capillary bed of the site of action.
- **Second order targeting**

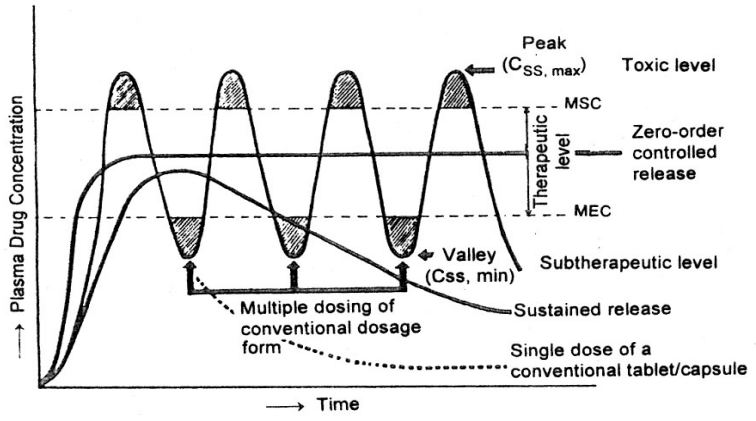
  Drug is delivered to special cell type (tumor cells).
- **Third order targeting**

  Drug is delivered to intracellular space of the target cells.

1.3. 3. Rationale of Sustained Drug Delivery[12]

The basic rational for Sustained drug delivery is to alter the pharmacokinetic and pharmacodynamic of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a dosing property of a rate controlled dosage form and less or not at all a property of the drug molecules inherent kinetics properties. Thus optional design of

controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamic of the drugs.[13]



A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

1.3.4. Ideal characteristic of the drug for the sustained release dosage form are

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.
- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

1.3.5. Attributes of successful sustained release dosage form design[14]

- The system should not be significantly sensitive to the physiological factors at the site of administration E.g. For oral systems, effect of pH, gastric motility, food and physical activity should be minimal.
- The mechanism of drug delivery should be based on the physicochemical Characters of the dosage form, rather than on the environmental factors of the host.
- The system should have a high degree of dispersion.
- The system should be specific to the area or the organ of interest.
- It should be easy to use and should have physical and chemical stability.

Potential advantage of sustained release dosage form[15]

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.
- Employ a less total drug.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Obtained less potential of reduction in drug activity with chronic use.
- Improved efficiency in treatment.
- Cure or control condition more promptly.
- Improved control of condition i.e. reduced fluctuation in drug level.
- Improved bioavailability of some drugs.
- Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.

- Overall, administrations of sustained release form enable increased reliability of therapy**.**

Disadvantages of sustained release dosage forms

- Possibility of dose dumping.
- Reduce potential for accurate dose adjustment
- Slow absorption may delay the onset of action.
- Increased potential for fist pass metabolism.
- Possible reduction in systemic availability.
- Drug release period restricted to residence time in gastrointestinal tract.

1.3.6. Factors governing the design of sustained release dosage form[16]

Drug related factors

- Aqueous solubility and pka
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and diffusivity

Biological factors

- Absorption
- Distribution
- Metabolism
- Biological half life
- Side effects and safety considerations
- Dose size

Physiological factors

- Prolonged drug absorption
- Variability in GI emptying and motility
- GI blood flow

Pharmacological factors

- Changes in drug effect upon multiple dosing
- Sensitizing /tolerance

Pharmacokinetic factors

- Dose dumping
- First pass metabolism
- Variability of urinary pH effect on elimination
- Enzyme induction /inhibition upon multiple dosing

1.4 .Classification of oral controlled release system[17]

a. Continuous release systems

1. Dissolution controlled release systems
    a. Matrix type b. Reservoir type
2. Diffusion controlled release systems
    a. Matrix type b. Reservoir type
3. Dissolution and diffusion controlled release systems
4. Ion exchange resin drug complexes
5. Slow dissolving salts and complexes
6. pH dependent formulations
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled systems

b. Delayed transit and continuous release systems

1. Altered density systems
    a. High density
    b. Low density
    c. Floating
2. Mucoadhesive systems
3. Size based systems

c. Delayed release systems

1. Intestinal release systems
2. Colonic release systems

1.4.1. Dissolution controlled release systems

Matrix tablets generally formulated by Embedded in a slowly dissolving or erodible matrix. Encapsulation or coating with slowly dissolving or erodible matrix substances.

1.4.2. Dissolution control formulations are categories as

a. Matrix dissolution control systems
b. Encapsulation or reservoir dissolution control systems

a. Matrix dissolution control systems

The matrix tablets are most often used for a drug-controlled release from a pharmaceutical dosage form. In this system for delay and control of the release of the Drug that is dissolved or dispersed throughout a rate controlling medium. They are very common used materials are Hydrophilic matrixes, Fat waxes, and Plastic matrixes. Which control drug dissolution by controlling rate of dissolution fluid penetration into the matrix by altering the porosity of table t, decreasing wettability by it self getting dissolved at a slower rate. The drug release is often first order from such matrixes.

Hence the following must be considered:

- The chemical nature of support (generally, the support are formed by polymers
- The physical state of drug (dispersed under molecular or particulate form or both)
- The matrix shape and alteration in volume as a function of time.

- The route of administration (oral administration remains the most widely used but other routes are adaptable .

Derivation of the mathematical model to describe this system involves the following assumptions:

- A pseudo steady state is maintained during drug release.
- The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
- The bathing solution provides sink conditions at all times.
- The diffusion coefficient of drug in the matrix remains constant i.e. no change in the characteristics of the polymer matrix.

Types of Matrix Tablets

There are 3 Types of Matrix Tablets

a. Hydrophilic matrixes

b. Fat wax matrixes

c. Plastic matrixes

a. Hydrophilic Matrixes[18]

Several commercial patented hydrophilic matrix systems are currently in use, such as synchronal technology and hydro dynamically balanced system.

e.g. Sodium Carboxy Methylcellulose, Methyl Cellulose, Hydroxy propyl Methyl Cellulose, Hydroxyl Ethyl cellulose, Polyethylene Oxide, Poly Vinyl Pyrrolidine, Poly Vinyl Acetate, Gelatin, Natural Gums etc.

Mechanism of drug release from matrix devices[19]

Sustained release oral products employing dissolution as the time limiting step are simplest to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a table t with a carrier that has a slow rate of dissolution.

In the dissolution process if the dissolution process is diffusion layer control, the rate of diffusion of drug from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting step. In this case the dissolution process at steady state would be described by Noyes-Whitney equation

$d_c/d_t = K_D A (C_s-C)$ ---------- (1)

Where,

d_c/d_t is dissolution rate.

K_D dissolution rate constant.

C_s is saturation solubility of drug.

C is the concentration of drug in bulk of the solution.

In relation to diffusion expression, that

$K_D = D/v*I$ ---------- (2)

Where, D is dissolution coefficient

V volume of dissolution media

I is the thickness of unstirred liquid film.

From the above expression it can be seen that the rate of dissolution i.e. availability is approx. proportional to the solubility of the drug in the dissolution media i.e. (C_s) provided a constant area and diffusion path length are maintained. This equation predicts constant dissolution rate as long as enough drug is present to maintain C_s constant, provided surface area does not change.

Advantages of hydrophilic matrix tablets:

- With proper control of the manufacturing process, reproducible release profiles are possible.
- The variability associated with them is slightly less than that Characterizing. Coated release form.
- Structure allows an immediate release of small amount of active principle there is no risk of dose dumping.
- Their capacity to incorporate active principle is large, which suits them to delivery of large doses.
- The manufacturing processes are notably simple. Table t formulation can be done via direct compression or by wet granulation techniques
- Large variety of non expensives gelling agents is approved for oral use by the competent official organization.
- The safety margin of high-potency drugs can be increased.
- The drug release from hydrophilic matrices show a typical time dependent profile i.e. decreased drug release with time because of increased diffusion path length.

Disadvantages of hydrophilic matrix tablets:

- Not suitable for water insoluble materials.
- Drug layering or drug coating is impossible.

b. Fat wax matrixes

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactants and spray drying techniques. Mechanism

- Delivery by diffusion.
- Delivery by surface erosion.

c. Plastic matrixes.

With plastic material(s) tablets can be easily prepared by direct compression of drug provided the plastic material can be comminuted (or) granulated to desired particle size to facilitate mixing with drug particles. e.g, Polyvinyl chloride, Polyethylene, Vinyl Acetate, Vinyl Chloride Copolymer, Acrylate or Methyl Methacrylate Copolymer, Ethyl Cellulose, Cellulose Acetate, Polystyrene.

1.4.3. Methods may be used to disperse drug and additives in the retardant base[19]

- A solvent evaporation technique can be used in which a solution /dispersion of drug and additive is incorporated into the molten wax phase. The solvent is removed by evaporation.
- Dry blends of ingredients may be slugged and granulated. more uniform dispersion, however, can be prepared by the fusion technique, in which drug and additive are blended into the molten wax matrix at temperatures slightly above the melting point.(e.g., approximately 90°c for carnauba wax.)
- The molten material may be spray congealed, solidified and milled, solidified and flaked or poured on cold rotating drum to form sheets, which are then milled and screened to form a granulation.
- The process used to prepare formulation for compression depends on the polymer and drug: polymer ratio.
- With high drug: polymer ratios, a wet granulation process is required. Low Milligram potency formulations may be directly compressed /granulated using alcohol if the polymer is not in a form amenable to direct compression**.**

1.4.4 . Materials used as retardants in matrix table t formulations

Table . 2

Matrix type	Retardants
Water insoluble inert materials	Polyethylene, Polyvinyl Chloride, Methyl Acrylate, Methacrylate Co-Polymer, Ethyl Cellulose.
Water insoluble erodible materials	Carnauba was, Stearyl Alcohol, Stearic acid, PEG, Hydrogenated Castor Oil, PEG Monostearate, Triglycerides.
Hydrophilic materials	Hydroxy Ethyl Cellulose, HPMC, Sodium CMC, Methylcellulose, hydroxy ethyl cellulose.
Natural polymers	Galactomannose (guar gum), chitosan, gum acacia, bean gum, sodium alginate, karaya gum, pectins, Xanthan gum.

1.4.5. Factors influencing the drug release from matrix

- Choice of matrix material.
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic material in aqueous system at a fixed concentration.
- Drug: matrix ratio and particle size of the drug.
- Table t hardness, porosity and density variation.
- Entrapped air in tablets.
- Table t shape and size.
- Solubility of drug in aqueous phase.
- Surfactants and other additives

B. Reservoir Dissolution Control Systems

This system containing an inner core of drug surrounded in a water insoluble polymer membrane. The polymer can be applied by coating or microencapsulation methods. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into surrounding fluid by diffusion. The polymers commonly used in such devices are Hydroxypropyl cellulose, Ethylcellulose and polyvinyl acetate. Disadvantage of the method is chance to sudden dose dumping which is not common with matrix tablets.

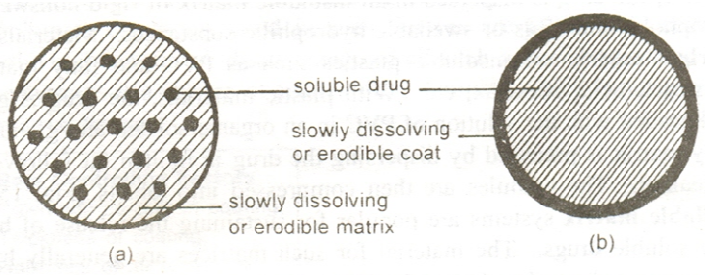


Fig.3: Schematic representation of dissolution controlled release systems – (a) matrix system, and (b) coated/encapsulated system

1.4.6. Diffusion controlled release20

Diffusion control formulations are categories as

a. Matrix Diffusion system

b. Reservoir Diffusion system

a. Matrix Diffusion system

The drug is dispersed in an insoluble matrix of rigid matrix of rigid non swellable hydrophobic material or hydrophilic materials. Materials used for rigid matrix are insoluble plastics materials with the plastic materials the drug is generally kneaded with the solution of plastic material in an organic solvent and granulated.

Waxy matrix is prepared by dispersing the drug in molten fat followed by congealing swellable matrix systems are popular for sustaining the release of highly soluble drugs e.g. the drug and gum are granulated together with a solvent such as alcohol and compressed in to tablets.

The release of the drug from such systems initially involves dehydrated hydrogels involves simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of a drug via swelling controlled diffusion mechanism. However during the swelling process equilibrium may not exist and diffusion may be non Fickinson diffusion.

In this system, a solid drug is dispersed in lipophillic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

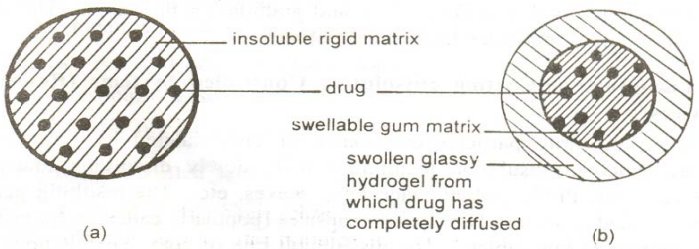


Fig.4 Diffusion controlled release systems – (a) rigid matrix, and (b) swellable matrix.

b. Encapsulation diffusion control

In this system water –insoluble polymeric material encases a core of drug. Drug will partition into the polymer membrane and exchange with the fluid surrounding the particle or table t.

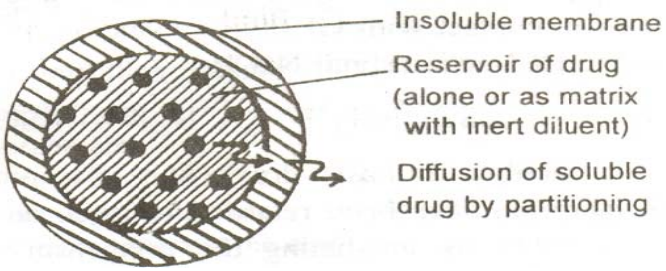


Fig.5 Drug release of diffusion across the insoluble membrane of reservoir device

[Desai, J (1966) Urquhart, J (1981)]

1.4.7. Release kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and it is practically evident in the case of matrix system. as a model dependent approach, the dissolution data are fitted to three popular release models such as zero order, first order, diffusion equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation.

a. Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released Vs time.

$$Q = K_0 t$$

Where,

Q is the fraction of drug released at time‘t’

K_0 = Zero order release rate constant

A plot of fraction of drug released against time will be linear if the release obeys zero order release kinetics.

B. First order release kinetics

Wagner assuming that the exposed surface area of the table t decreased exponentially with time during dissolution process suggested that drug release from most slow release tablets could be described adequately by apparent first-order kinetics. The equation used to describe first order kinetics is

$$\ln (1-Q) = - K_1 t$$

Where

Q = Fraction of drug released at time't'

K_1 = First order release rate constant

Thus, a plot of logarithm of the fraction of drug remained against time will be linear if the release obeys first order kinetics.

c. Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = K_2 t^{1/2}$$

Where

Q = Fraction of drug released at time't'

K_2 = release rate constant

A plot of fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on Fick's law, square root of time dependent.

1.4.8. Principle of modified drug release

Following either of the two principles can modify drug release

a. Barrier principle

In this method the retardant material is imposed between the drug and elusion medium. Drug release is by diffusion of the drug through the barrier and /or erosion of the barrier or permeation of the barrier by moisture.

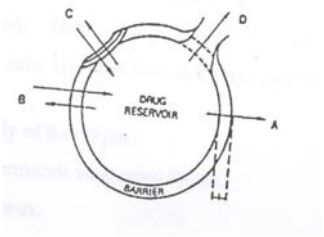


Fig: 6 Drug diffusion through the barrier, B.permeation of barrier by elution media followed by drug dissolution. C, Erosion of barrier releasing drug, D ruptures of permeation of elution media**. [Manion C.V (1977) Welling.G (1978)]**

b. Embedded matrix

In this drug is dispersed embedded in a matrix of retardant material that may be encapsulated in a particulate form or compressed into the table t. Drug release occurs by permeation of water leaching extraction of diffusion of drug from the matrix and erosion of the matrix and erosion of matrix material.

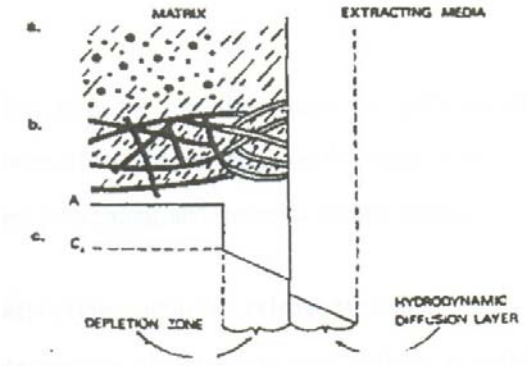


Fig: 7 Embedded matrix concept as a mechanism of controlled released in sustained release dosage form design network model a drug is insoluble in the retardant material. B Drug is soluble in the retardant material. **[Wu .JC (1993), Alfrey .TJR (1966)]**

1.4.9. Recent trends in sustained drug delivery system

Sustained release dosage forms are categorized as

A. Single unit dosage form.

B. Multiple unit dosage form.

C. Mucoadhesive system.

A. Single unit dosage form:

These refer to diffusion system where the drug is uniformly distributed (dispersed dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film. These systems can be classified as:

a. Monolithic system:

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is rate- limiting step.

b. Hydrophobic/Swellable table t:

Table t prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the release time of the drug from device within the GI tract after oral administration.

c. Floating table t or capsule:

Designing of Floating table t or capsule are called hydro-dynamically balanced drug delivery system is based on the principle that device with gravity lesser than that of the gastric juice of stomach and retain the drug in the proximal region of the GIT.

d. Semisolid matrix system:

In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

e. Coated table t and Similar Multilayer system:

Multilayer systems are designed in such a way that the drug has to cross a barrier or membrane on its way from the device to the physiological environment. The nature and the number of barriers control the release process.

In the simplest form coated table t comprised a core containing the drug and a coating layer, which surrounds the core. The core is usually the drug either alone or loaded on to an inert material (hydrophilic or hydrophobic).

Multilayered table t having two or more distinct layers usually prepared by dry coating technique have also been used to formulate sustained or controlled preparations for water-soluble drugs. In this case, coating which controls the release process covers the core table t containing the drug only partially.

f. Osmotic device:

In osmotic device usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment that is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice.

B. Multiple unit dosage forms:

It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drugs or part of the same drug immediately

While remaining drug or parts of the same can be sustained release. These are useful where drug-Excipients and drug-drug interactions are inevitable in a single unit dosage form.e.g. are Micro ranules / Sphéroïdes, Beads. Pellets. Micro capsules.

C. Mucoadhesive systems:

It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is definable as the occurrence in which one biological substance is adhered to another substance, which may either, be of biological or non-biological origin. If the substance is mucosal membrane the phenomenon is known as mucoadhesion.

2. AIM AND OBJECTIVE

Need for the study

Over the last three decades sustained release technology has received increasing attention from the pharmaceutical industry due to its increased clinical value as well as extended product life. Treatment of a disease or infection in most cases requires maintaining a desired drug plasma concentration level over a prolonged period of time. Such clinical needs often are satisfied by a multiple dose therapy, which can involve frequent dosing of two to four doses per day. It can be very difficult for patients to stick to such stringent routines, which can lead to poor patient compliance and, consequently, the desired drug plasma concentration level can be below the acceptable minimum therapeutic concentration. This can lead to inadequate relief and/or the development of a tolerance to the drug.

The most common approach to minimizing patient noncompliance is by using extended release drug delivery system to decrease the number of doses that must be taken each day. One useful approach in this regard involves using a polymer based matrix in which the drug is uniformly dispersed or dissolved. Approach for higher doses (based on weight) and prolonged release formulations are challenging task in formulation development. Hence, there is still a need in the art for modified release dosage based formulation.

Objectives

- The main aim of the present work is to formulate and evaluate sustained release matrix tablets of metformin (750mg) using 5 different polymers of 4 different concentration (20,25, 30 & 35%).
- To estimate the physio-chemical properties and *invitr*o drug release profile of the formation with the innovator (Glucophage XR)
- To choose the best drug formulation from the above evaluations.
- To subject the most satisfactory formulation based on the above studies for accelerated studies.

3. LITERATURE REVIEW

1. Shukka Taphan, et al.,[22] carried out a research work to develop an extended release metformin Hcl tablet and to study effect of additives on the drug release mechanism . The polymer used is the HPMC K 100 M .The polymer ratio is 3.3 :1 gives 91 % drug release over 11 hour study in non linear fraction . Water up takes study showed that HPMC had a slow hydration and swelling rate in non linear fashion during the first hour. After 1 hour showed a linear up take profile. Metformin with soluble or in soluble additives with HPMC showed lower swelling compared to tht of metformin hcl with hpmc tablet (reference) in soluble additives are mcc, dcp, starch . Soluble additives are Nacl, lactose, an hydrous pregelatinized starch, sls, providone.

2. Dinda, et al.,[23] carried out a research work to design a formulation to improve the oral therapeutic efficiency with optimal control of plasma drug level which contains two anti diabetic drug metformin and glimepridine . metformin sustained release and glimepride an immediate release as a bi layer tablet . Two formulations with hydrophilic swellable polymer and other with hydrophobic polymer for sustained delivery from matrices. hydroxyproplymethylcellulose and polyethylene oxide used as polymer for sustained release.

3. Milind Janrao Umekar, et al.,[24] studied to develop the oral sustained release metformin hydrochloride tablet formulations using lipophilic waxes such as hydrogenated caster oil , stearic acid and glyceryl mono sterate either alone or their combinations by melt granulation . The drug release kinetics demonstrated that hydrogenated caster oil sustained the release of metformin grater than the stearic acid and glyceryl mono sterate.

4. Jaime Davidson and Harry Howlett[25] studied the new prolonged release metformin improves gastro intestinal tolerability . metformin mainly administrated to patients with type 2 diabetes , but side effect may be high such as gastrointestinal side effects and complex administration regimen . New prolonged release metformin formulation (GLUCOPHAGE SR) , given once daily in placebo controlled trials . It lowers the side effect . The improved

tolerability associated with prolonged release metformin probably arises from the tablet design , which releases metformin in to the upper intestine by diffusion from a dual hydrophilic polymer matrix (Gel shield diffusion system) . This provides slower , smoother and longer drug delivery , with out an initial rapid rise in plasma metformin.

5. Milind J, et al.,[26] studied the formulation and evaluation of sustained release matrix tablet of metformin hydrochloride using ph dependent and ph independent methacrylate polymers , by direct compression of drug and different ph dependent Eudraget L100 and S 100 and ph indipentent Eudraget RLPO and RSPO polymer combinations . evaluation provided that S IOO RLPO and S100 / RSPO mixture give maximum sustained action .

6. Sundaramoorthy. K, et al.,[27] studied the in vitro and in vivo release of metformin SR tablets , ethyl cellulose as the polymer. Concentrations of drug vary and polymer constant. The drug polymer ratio 5:3 more successful of study.

7. Natalie Foster and Kyle A Fliszar[28] studied a continuous dissolution/absorption system using a hexadecane membrane (HDM) as the permeation measurement has been examined for 3 distant formulations of Metformin HCL . this system was used to correlate the absorption rate of metformin through the membrane after release from the dosage form to rate of the appearance of metformin in the plasma from the same formulation.

8. David Stepensky and Michael Friedman[29] studied the pharmacokinetic (PK) and pharmacodynamic (PD) rationales to develop controlled release(CR)formulations of metformin. Unrestrained diabetic rats received the drug as intravenous bolus (i.v.), oral solution (p.o.),intra-duodenal bolus, 4-h infusion, or intra-colonic bolus. In addition, we developed two CR-gastroretentive dosage forms(CR-GRDF) that released the drug over 3 or 6 h (in vitro), and retained in the rats' stomach for 8–10 h. Metformin exhibitedflip-flop PK. The colonic absorption was low but sustained and was associated with highly variable glucose-lowering effects,thus providing a PK rationale to develop CR-GRDF. In addition, the glucose-lowering effect was greater following p.o. vs.i.v. administration, despite equivalent AUC, indicating a first pass PD effect, thus, adding a PD rationale to

developmetformin CR-GRDF. When administered to the diabetic rats, CR-GRDFs produced bioavailability and extent of glucoseloweringeffects that were similar to those of the duodenal infusion and p.o. metformin administration. These findings areattributed to the adsorption of metformin to the intestine that yields slow and prolonged absorption even following p.o.administration of drug solution. The data indicates that unless the CR formulation could significantly extend the absorptionperiod, it is not likely to improve glucose-lowering efficacy

9. Saptarshi Dutta, et al.,[30] formulate the oral sustained release Metformin hydrochloride matrix tablets by using hydroxyl methyl cellulose polymer (HPMC) as rate controlling factor and to evaluate drug release parameters as per various release kinetic models. It is observed that the basic goal of therapy in the development of Metformin hydrochloride release dosage form is to increase bioavailability; reduce risk of hospitalization, deliver drug at a near constant rate for approximately 12 hrs, independent of food intact and gastrointestinal PH. The dry granulation technique was used to compress the tablet as powder showed the poor flowability; less cohesiveness during direct compression and due to moisture sensitivity and tendency to hydrolyte, wet granulation techniques was not selected for the present work. Dry granulation improves the flow of the powder and reduces the use excipients. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, drug content etc. and showed satisfactory results. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in vitro release studies. The in vitro dissolution study was carried out for 12 hours using PH 4.0, 6.8 Phosphate buffer & pH 1.2 buffer in phosphate buffer as dissolution media. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications. The mechanism of drug release form matrix tablet is govorenered by diffusion and as the drug is so highly soluble. However, when considering in-vivo behavior of this system, the erosion rate will be more important.

10. Paola Mura, et al.,[31] had investigated because of low bioavailability and short half-life of metformin hydrochloride (MH) make the development of sustained-release forms desirable. However, drug absorption is limited to the upper

gastrointestinal (GI) tract, thus requiring suitable delivery systems providing complete release during stomach-to-jejunum transit. This study was undertaken to develop a MH sustained-release formulation in compliance with these requirements. The strategy proposed is based on direct-compressed matrix tablets consisting of a combination of MH with the hydrophobic triacetyl-β-cyclodextrin (TAβCD), dispersed in a polymeric material. Different polymers were tested as excipients, i.e. hydroxypropylmethylcellulose, xanthan gum, chitosan, ethylcellulose, Eudragit®L100-55, and Precirol®. Compatibility among the formulation components was assessed by DSC analysis. All the tablets were examined for drug release pattern in simulated gastric and jejunal fluids used in sequence to mimic the GI transit. Release studies demonstrated that blends of a hydrophobic swelling polymer (hydroxypropylmethylcellulose or chitosan) with a pH-dependent one (Eudragit®L100-55) were more useful than single polymers in controlling drug release. Moreover, the main role played by the MH-TAβCD system preparation method (i.e. grinding or spray-drying) in determining the behaviour of the final formulation was evidenced. In fact, for a given matrix-tablet composition, different sustained-release effects were obtained by varying the relative amounts of MH-TAβCD as ground or spray-dried product. In particular, the 1:1 (w/w) blend of such systems, dispersed in a Eudragit–chitosan polymeric matrix, fully achieved the prefixed goal, giving about 30% released drug after 2 h at gastric pH, and overcoming 90% released drug within the subsequent 3 h in jejunal fluid.

11. Lian – Dong Hu, et al.,[32] In this study, metformin hydrochloride (MH) sustained-release pellets were successfully prepared by centrifugal granulation. Seed cores preparation, drug layering, talc modification and coating of polymeric suspensions were carried out in a centrifugal granulator. Talc modification was performed before coating in order to overcome the high water solubility of metformin. The influence of surface modification by talc, the effects of Eudragit® types and ratios, as well as the correlation between in vitro release and in vivo absorption were investigated in detail. Experimental results indicated that talc modification made a decisive contribution to controlling the drug release by avoiding drug dumping. Three dissolution media: 0.1 M HCl, distilled water and pH 6.8 phosphate buffer were employed to determine the in vitro release

behaviors of the above metformin hydrochloride pellets. The relative bioavailability of the sustained-release pellets was studied in 12 healthy volunteers after oral administration in a fast state using a commercially available immediate release tablet (Glucophage) as a reference. Following coating with a blend of Eudragit® L30D-55 and Eudragit® NE30D (1:20), at 7% or 10% coating level, respectively (referred to as F-2, F-3), the pellets acquired perfect sustained-release properties and good relative bioavailability. The C_{max}, T_{max} and relative bioavailability for F-2 and F-3 coated pellets were 1.21 μg/ml, 6 h, 97.6% and 1.65 μg/ml, 8 h, 165%, respectively. Combined use of two Eudragit® polymers with different features as coating materials produced the desired results. Restricted delivery of metformin hydrochloride to the small intestine from differently coated pellets resulted in increased relative bioavailability and a sustained release effect. The adoption of several different pH dissolution media established a better relationship between the in vitro release and in vivo absorption of the sustained-release pellets.

12. Kulang – Hee Shin, et al.,[33] studied the combination of glimepiride and metformin is used for glycemic control in patients with diabetes mellitus. A fixed-dose combination of glimepiride/metformin 2/500 mg slow-release (SR) formulation was developed to improve compliance in polymedicated patients. To accommodate the various dosing regimens of glimepiride, a glimepiride / metformin 1/500 mg SR tablet was also developed

13. Sfalchi, et al.,[34] had studied the Oral absorption of the antihyperglycaemic agent metformin (MF·HCl) is confined to the upper part of the intestine, therefore controlled-release oral formulations of this drug should ensure a complete release during transit from stomach to jejunum. Compressed matrix tablets based on pH-sensitive poly(ethylene oxide) (PEO)–Eudragit L100 (EUD L) compounds have shown in vitro a compliance with the above requirement. The polymer compounds were prepared by a coevaporation process. The release pattern of MF·HCl from matrices depended on the PEO–EUD L ratio in the coevaporate. The 1:1 (w/w) ratio was unable to control MF·HCl release in simulated gastric fluid (SGF, pH 1.2), because the matrix material was excessively hydrophilic. Nevertheless, the release rate in SGF could be modulated by increasing the EUD

L fraction in the coevaporate. With a PEO (M_w, 400 kDa)–EUD L (1:2, w/w) ratio the percent dose released in 2 h to SGF, where the coevaporate was insoluble, was around 23 or 50% with 10 or 20% loading dose. The release was then completed within the successive 2 h of elution with simulated jejunal fluid (SJF, pH 6.8) where EUD L and the coevaporate gradually dissolved. Release in SGF was controlled by matrix swelling and/or drug diffusion in matrix, whereas matrix dissolution controlled release in SJF. The unique release-controlling properties of the polymer compounds were due to PEO–EUD L macromolecular interactions. Matrices show promise of a gradual and complete release of MF·HCl from stomach to jejunum, unaffected by gastric pH fluctuations. This mode of administration might allow the use of lower therapeutic doses compared to existing immediate- or sustained-release products, thus minimising side effects.

14. Anil K Babbar, et al.,[35] the objective of the present study was to develop a hydrodynamically balanced system of metformin as a single unit floating capsule. Various grades of low-density polymers were used for the formulation of this system. They were prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the basis of *in vitro* buoyancy and *in vitro* release in simulated fed state gastric fluid (citrate phosphate buffer pH 3.0). Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best *in vitro* percentage release and were taken as the optimized formulation. By fitting the data into zero order, first order and Higuchi model it was concluded that the release followed zero order release, as the correlation coefficient (R^2 value) was higher for zero order release. It was concluded from R^2 values for Higuchi model that drug release followed fickian diffusion mechanism. *In vivo* studies were carried out in rabbits to assess the buoyancy, as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy. The formulation remained buoyant during 5 h of study in rabbits. The comparative pharmacokinetic study was performed by administration of the optimized HBS capsules and immediate release capsules, both with radiolabeled metformin,

using gamma counter. There was an increase in AUC in optimized HBS capsules of metformin when compared with immediate release formulation.

15. Kamlesh J Wadher, et al.,[36] studied metformin hydrochloride has relatively short plasma half life, low absolute bioavailability. The need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release formulations that would maintain plasma level for 8 -12 h might be sufficient for daily dosing of meformin. The overall objective of the present work was to develop an oral sustained release metformin tablet prepared by direct compression method, using hydrophilic Eudragit RSPO and RLPO alone or in combination with hydrophobic ethyl cellulose polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and *in vitro* drug release. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. When Endragit RSPO and RLPO were used alone as the only retarding polymer, a sustained drug release pattern were not observed while, Inclusion of ethylcellulose in the matrix almost doubled (12 h) the time required for releasing the drug. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled to anomalous type. Fitting the data of Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

5. DRUG PROFILE

Drug Class

Anti diabetic drug

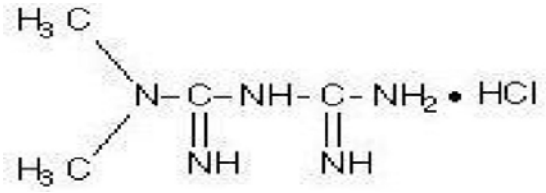
METFORIMIN HYDROCHLORIDE[37]

Chemical Name - N,N-dimethylimidodicarbonimidic diamide hydrochloride

Empirical Formula - $C_4H_{11}N_5$

Molecular Weight - 165.63

Structural Formula -



Category - Oral Anti hyperglycaemic

Appearance - While Crystal

Solubility - Freely Soluble in Water, Slightly Soluble In Alcohol ,Insoluble In Acetone And Dichloromethane

ADR - Distributed to mother milk and had effect on infants

Pharmaco Kinetics - Slowly Absorbed by GI tract, 500mg Drug→ 50-60% Absorbed again reduced when taken with food

HALF LIFE→2 TO 6 HOURS[37]

Mechanism

- Decrease the glucose tolerance
- Decrease hepatic glucose production
- Decrease intestinal absorption of glucose
- Improves insulin sensitivity by increasing peripheral glucose uptake and utilization

BRANDS

- Glucophage
- Fortamet
- Riomet

Pharmacokinetics & Pharmacodynamics

Absorption

It is rapidly absorbed after oral administration with peak plasma or serum concentrations appearing within1.5-2 hours .oral absorption is estimated to be 80% of the dose.

Metabolism[37]

The drug rapidly metabolized through oxidation and glucuronic acid conjucation with urinary excretion of inactive metabolites usually complete within 24 hours.

Mechanism of action[37]

Metformin is an anti hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Excretion

Less than10% of administered NSAIDS is eliminated in urine.

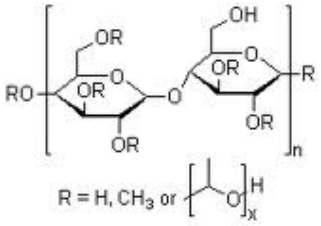
Plasma half life

6.2 hours.

6. EXCIPIENTS PROFILE

6.1. Hydroxy Propyl Methyl Cellulose[38]

Structure



Molecular Formula : $C_{56}H_{108}O_{30}$

Molecular Weight : 3912.39

Description : White of white powder

Solubility

Swells in cold water , in soluble in hot water , soluble in most organic solvents.

Melting Point

56.2°C

Density

1.39g/cm3

Chemical Properties

Hpmc is cellulose either, derived from alkali treated cellulose that is reacted with methyl chloride and propylene.

USE

HPMC is an enteric film coating material or a matrix binder in solid dosage forms. It is used as a viscosity control agent, gelling agent, film former, stabilizer, dispersant, lubricant, binder, emulsifying agent and suspending agent end applications include adhesieve, building materials , personal care products, detergents and surfactants, printing and coatings , pharmaceutical food products , polymerization and textiles.

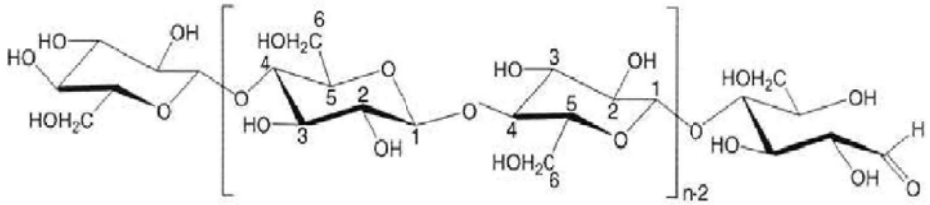
Different grades of HPMC

Typical viscocity values for 2% (W/V) aqueous solution of methocel (Dow Chem. Co.) viscosity measured at 20°C.

Methocel Product	USP 28 designation	Normal Viscosity
Methocel K100M	2208	100
Methocel K15M	2208	15000
Methocel K4M	2208	4000

6.2. Micro Crystalline Cellulose[39]

Structure



Non-Proprietary Names

- BP . micro crystalline cellulose
- JP . micro crystalline cellulose
- Ph EUR . cellulosum microcrystillinum
- US PNF . micro crystalline cellulose

Synonyms : Avicel ph, celex; cellulose gel, crystalline cellulose, E4 60 , emocel , Ethispheres , fibrocel , pharmacel , Tabulose , vivapu .

Chemical Name : Cellulose

Empirical Formula : $C_6H_{10}O_5$

Functional Category : Adsorbent , suspending agent , tablet and capsule diluents , tablet disintegrent .

Application in Pharmaceutical Formulation and Technology

MCC is widely used in pharmaceutical formulations as binder , diluents in oral tablet and capsule . Where it is used in both wet-granulation and direct compression

process. In addition to it is used as binder, diluents. Micro crystalline cellulose also had some lubrication and disintegrates properties that make it useful in tabletting.MCC is also used in cosmetics and food products.

Description

Microcrystalline cellulose is purified partially depolymerized cellulose that occur as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size and moisture grades that have different properties and applications.

Typical Properties

Angle of repose	-	49 degree for ceolus KG 34.4 degree for emcocel 90 M
Flow Ability	-	1.41 gls for emocel 90 M
Melting Point	-	Chars at 260-270 degree Celsius
Moisture Content	-	Typically less than 5% w/w however different grades may contain varying amount of water.MCC is hydroscopic.

Particle Size Distribution

Typical mean particle size is 20 to 200 micrometer

Solubility

Slightly soluble in 5 % w/v of Sodium hydroxide solution practically insoluble in water , dilute acids and most organic solvents .

Use Of MCC

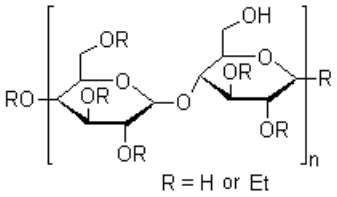
USE	CON %
Adsorbent	20 - 90%
Anti adherent	5 – 20%
Capsule binder/diluents	20 – 90%
Tablet disintegrant	5 - 15%
Tablet binder / diluents	20 -90%

Stability And Storage Conditions

MCC is stable through hydroscopic material. The bulk material should be stored in a well closed container in a cool, dry place.

6.3. ETHO CEL[40]

Structure



Synonym - Cellulose Ethyl Ether e462 ,Surlease , Ethyl Cellulose

Preparation

Prepared from wood pulp or by chemical treatment with alkali and ethylation of the alkali cellulose with ethyl chloride.

Functional Category

Counting agent, tablet binder viscosity-increasing agent .

Description

Ethyl cellulose is tasteless, free flowing

Typical Properties

Practically insoluble in glycerin, propylene glycol and water. Ethyl cellulose contains less than 46.5% of ethoxy group is freely soluble in CHCL3 . Methyl acetate, tetra hydrocarbons with ethanol 95% . ethyl cellulose that is freely soluble in chloroform, ethanol 95% ethyl acetate , methanol and toluene .

Viscosity

Various grades of ethyl cellulose are commercially available which differ in their ethoxy content and degree of polymerization. The viscosity of solutions increases with an increase un concentration of ethyl cellulose.

Stability and Storage Conditions

Ethyl cellulose is a stable, slightly hydroscopic material . it is chemically resistant to alkali , both dissolve and concentrated and to salt solution, although it is more sensitive to acidic materials than cellulose ester. Ethyl cellulose is subjected to oxidation in the presence of sunlight or uv light at elevated temperature .this may absorption properties between 230 to 340 nm .the bulk materials should be stored in a dry place in a well closed container.

Safety

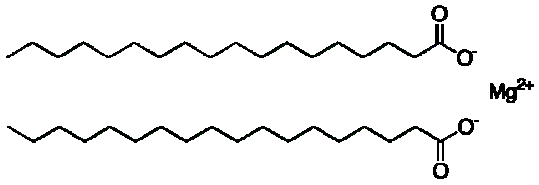
Ethyl cellulose is a stable, slightly hydroscopic material. It is chemically resistant to alkali. Although it is more sensitive to acidic materials than cellulose esters .Ethyl cellulose is subjected to oxidative degradation in the prescience of sunlight or UV light at elevated temperature. This may be prevented by the use of an antioxidant and a compound with light absorption properties between 230-340 nm. The bulk materials should be stored in a dry place, in a well closed container.

Use

Ethyl cellulose is widely used in oral and topical pharmaceutical formulation. It is used in food products. Ethyl cellulose is not modified following oral conception and is there for a non caloric substance. In general it is regarded as a non toxic non allergenic and non irritant material. Since ethyl cellulose is not metabolized it is recommended for using parental products.

6.4. Magnesium Sterate[41]

Structure



Non Proprietary Name

BP - Magnesium sterate

JP -Magnesium sterate

Ph EUR-Magnesi steares

USPNF-Magnesium state

Synonym **:** Magnesium octade canoate , octadecanonic acid , Magnesium salt

Chemical Name CAS Registry Number **:** Octade canoic acid magnesium salt (557-04-10)

Empirical Formula and Molecular Weight: C_{36} H_{70} MgO_4 (591 .34)

The USPNF 23 describes magnesium sterate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium sterate and magnesium palmitate (C32H62MGO4) . The ph EUR 2005 describes magnesium sterate as a mixture of magnesium salt of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids .

Structural Formula

$(CH_3 (CH_2)_{16}COO)_2mg$

Factional Category

Tablet and capsule lubricant

Application in Pharmaceutical Formulation And Technology

Magnesium sterate is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture of concentrations between 0.25% and 5.0 w/w

Description

Magnesium sterate is very fine , light weight ,precipitated or milled , implantable powder of low bulk density , having a faint odor of stearic acid and a characteristic taste . The powder is greasy to touch and readily adheres to skin.

Melting Point

117 – 150°c (commercial samples)

126 – 130°c(highly purity magnesium sterate)

Solubility

Practically in soluble in ethanol , ethanol(95%) either and water . slightly soluble in warm benzene and warm ethanol (95%)

Stability and Storage Conditions

Magnesium sterate is stable and should be stored in a well closed container in a cool , dry place .

6.5. POLYOX WSR 300[42]

Non Proprietary Name

USPNF ; Polyethylene Oxide

Synonyms

Polyox , Polyoxirane , polyoxyethylene

Description

- White off white
- Free flowing
- Slightly ammonical odour

Chemical name

Polyethylene oxide

Molecular weight

7000000

Strectural formula

(CH2CH2O)n n is the no of oxyethylene gou

Application

Mucoadhersive polymer , Tablet binder(5 – 85%) , Thicknening agent , In higher molecular weight it is used as a sustained release polymer via the hydrophilic matrix approach

Deferent grades

- WSR N - 10
- WSR N -80
- WSR N -750
- WSR N - 3000
- WSR N -1105
- WSR N - 12K
- WSR N – 60K
- WSR N – 301
- WSR coagulant
- WSR 300

4. METHODOLOGY

4.1. Materials and Methods

List of Excipients and their Functions

Table: 3

Sl no	Ingredients	Function
1	Methocel K100M	Polymer
2	Methocel K15M	Polymer
3	Methocel K4M	Polymer
4	Ethocel 20 prem	Polymer
5	Polyox WSR 300	Polymer
6	MCC Ph 101	Diluents

List of equipments used

Table : 4

Equipment	Manufacturing company
Electro balance	**Mettle Toledo , USA**
Bulk density apparatus	**Electrolab , mumbai**
Rapid mixer granulator	**Anchor , mumbai**
Double cone blender	**Erweka**
Rotary tablet punching machine	**Rimek , mumbai**
Friability test apparatus	**Electro lab , Mumbai**
Tablet hardness tester	**Schleniger hardness tester**
Fludised bed drier	**Anchor mumbai**
Disintegration test apparatus	**Electro ,mumbai**
Sonic swifter	**Erweka**
Tablet dissolution apparatus	**Electrolab , mumbai**
Helium lamp (LOD)	**Mettler , taledo**
Thickness (vernier calipers)	**Mitutogo vernier calipers**
Stability chambers	**Thermo lab**
Hot air oven	**Eltek motors mumbai**
Hplc	**Ezchrom Elite**

4.2 INNOVATOR DETAILS

GLUCOPHAGE - metformin hydrochloride tablet, film coated

GLUCOPHAGE XR - metformin hydrochloride tablet, extended release

Bristol-Myers Squibb Company

Active Incredent	:	Metformin Hydrochloride
Dosage Form (oral)	:	Tablet , Extended Release
Proprieky Name	:	Glucophase XR
Applicant	:	Bristal Myers Squibb
Strength	:	500 mg
Applicant No	:	21202
Product No	:	001
Approval Date	:	Oct 13 , 2000
Ref listed Drug	:	Nil

Description

GLUCOPHAGE® (metformin hydrochloride) Tablets and GLUCOPHAGE® XR (metformin hydrochloride) Extended- Release Tablets are oral antihyperglycemic drugs used in the management of type 2 diabetes. Metformin hydrochloride (*N, N* dimethylimido dicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti hypo glycemic drug.

GLUCOPHAGE tablets contain 500 mg, 850 mg, or 1000 mg of metformin hydrochloride. Each tablet contains the inactive ingredients providone and magnesium stearate. In addition, the coating for the 500 mg and 850 mg tablets contains hypromellose andthe coating for the 1000 mg tablet contains hypromellose and polyethylene glycol.

GLUCOPHAGE XR contains 500 mg or 750 mg of metformin hydrochloride as the active ingredient.

GLUCOPHAGE XR 500 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose,hypromellose, microcrystallinecellulose, and magnesium stearate.

GLUCOPHAGE XR 750 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hypromellose, and magnesium stearate.

System Components and Performance–GLUCOPHAGE XR comprises a dual hydrophilic polymer matrix system. Metforminn hydrochloride is combined with a drug release controlling polymer to form an "inner" phase, which is then incorporated as discrete particles into an "external" phase of a second polymer. After administration, fluid from the gastrointestinal (GI) tract enters the tablet, causing the polymers to hydrate and swell. Drug is released slowly from the dosage form by a process of diffusion through the gel matrix that is essentially independent of ph. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the faeces as a soft, hydrated mass.

Fig:8 – Glucophage Wrapper

Dissolution Data of Glucophage XR 750

Table -5

Time	Release
1 HR	**31**
2 HR	47
3 HR	59
5 HR	75
7 HR	87
10 HR	96
REC	97

1 hr 22 - 44 %
3 hr 49 - 69%
10 hr NLT 85%

The physical compatibility test between drug and other tablet components was carried out at moderate, intermediate, and extreme conditions for specified period of time. The mixture does not show any visible changes, this indicates that drug and other tablet components did not have any physical compatibility.

4.3. Evaluation of Reference Product

The following tests were performed for the reference product.

a) Weight variation
b) Thickness
c) Hardness test
d) Friability test
e) Assay
f) *In-vitro* Release Study

a. Weight Variation

Method:

Twenty tablets had been collected and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The weight variation limits are given in below table.

Table : 6 Weight variation table

Average weight of table t (X mg)	Percentage Deviation
80 mg or less	10
80mg to 250mg	7.5
more than 250 mg	5

b. Thickness

Twenty tablets had been collected and each table t thickness was measured by using venire caliper. The allowable limit is ± 0.3%.

c. Hardness

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. If the table t is too hard, it may not disintegrate in the required period of time and if it is too soft, it will

not withstand the handling during coating, packaging and shipping operations. Hardness was measured using hardness tester. For each batch three tablets were tested and mean was calculated.

d. Friability

Friability is a table t property that evaluates the ability of the table t to withstand abrasion in packaging, handling and shipping.

Twenty tablets had weighed and placed in the Roche Friabilator. Then, it was operated at 25 RPM for 4 minutes. The tablets were dedusted and reweighed after 100 revolutions. Friability of the tablets is not more than 1% of their weight**. [Leon Lachman (1976)]**

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

e. Dissolution test

Dissolution is the process by which a solid substance enters the solvent phase to yield a solution. Adequate oral bioavailability is a key pre-requisite for any orally administered drug to be systemically effective. Dissolution is of primary importance for all conventionally constructed; solid oral dosage forms in general, and can be the rate limiting step for absorption of drugs which are administered orally. Here the dissolution is performed in USB paddle apparatus and the percentage release is identified by HPLC method.

f. Assay

Assay is mainly used for the determining the amount of drug content in the tablet. This identified by HPLC method and compared with the standard.

4.4. EVALUATION OF METFORMIN HYDROCHLORIDE

Identification Of Metformin Hydrochloride

Description	:	A white crystal
Solubility	:	Freely soluble in water , slightly soluble in alcohol , Insoluble in acetone and Dichloro methane .
Melting Point	:	123°C
pH	:	6.8 IN A SOLUTION OF 1%
Loss of drying	:	Dry in vacuum at 60`c for 4 hours, it loses more than 0.5% Of this weight

4.5. Assay of Metformin Hydrochloride

Standard Preparation: Metformin Hydrochloride working standard equivalent to 50 mg were taken into100ml volumetric flask and it was diluted with Methanol and acetonitrile and mixed.

Test Preparation: Twenty tablets had taken then powdered, weight powdered table equivalent to 50mg metformin and transfer into 100ml volumetric flask and dilute with the methanol and acetonitrile. The actual drug content of Metformin layer containing the polymer was carried out by HPLC (High Performance Liquid Chromatography, 2695 waters). INERTESIC 50DS-2, 250mm length, 4.6mmID column and 5mm particle size. Flow rate 1.2ml per minutes, load 10, at wavelength 233mm with run time 15 minutes.

Mobile phase – 10mM acus octain-1-sulphonic acid Na salt solution at ph3 and Acitonitrile at a propotion of 80:20. Injection volume -5 micro litre.

4.6. Dissolution of Metformin Hydrochloride Tablets

In vitro dissolution studies for all the compressed tablets were carried out using paddle method at 100 rpm in 900 ml of 6.8 pH phosphate buffer at 37°c ± 0.5°c. A sample was withdrawn at 1, 2, 3, 5, 7, 10 hours respectively and is filtered through filters and assayed by HPLC method . An equal volume of fresh medium which was pre warmed at 37°c was replaced in to the dissolution medium after each sampling to maintain the constant volume throughout the test.

Mobile Phase And Chromatographic System

Procedure: Injected an accurately measured volume (about 5 ml) of a filtered portion of the solution under test in to the chromatogram by means of sampling vials. Record the chromatogram and measure the response of the major peak. Calculated metformin hydrochloride dissolved in comparisons with a standard solution having a known concentration of metformin hydrochloride USP in the same medium.

4.7. FORMULATION OF METFORMIN HYDROCHLORIDE (750mg) SUSTAINED RELEASE TABLETS

Twenty formulations were prepared by wet granulation method using 5 different polymers in 4 different concentrations (20% , 25% , 30% , 35%) and the formulation were named as (F1 F2…….F20) .

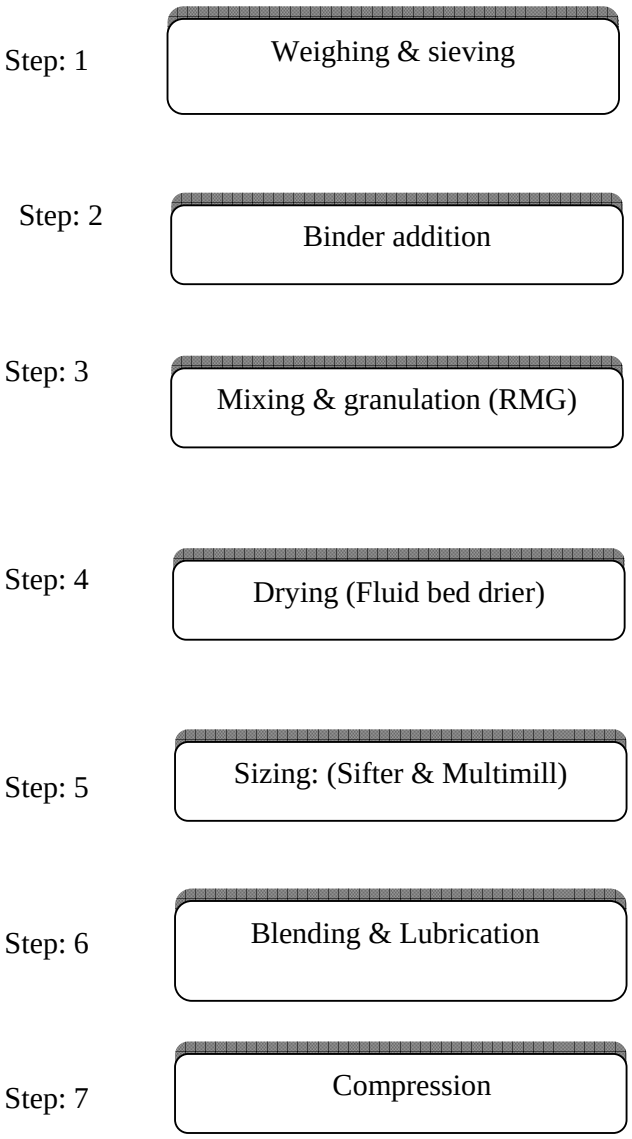
Procedure

The ingredients are shown in the table no -

- Weigh ingredients 1,2,3 and pass through 22 sieve
- Add ingredients 1 to ingredient 2 in RMG while dry mix followed by ingredient 3
- Granulate the above blend using water as per parameters specified
- The above granules are semi dried and are passed through cutter mill for breaking of lumps
- The above granules are dried to get required LOD
- Dried granules are passed through multi mill (cutter) and are passed through 20 sieve
- Thus obtained blend is lubricated with mg sterate (#60pass)
- The above blend is compressed using 21*10mm with specified parameters

4.8. Formulation Development Trials

Process Flow Chart



4.9. Formulation Table

Table -7

	Formulation Code	Metformin	Polymer concentration	MCC pH 101	Mg Ster	Water (ml)	Total Wt
Methocel K100M	F1	750	20%	150	5	400	1055
	F2	750	25%	112.5	5	400	1055
	F3	750	30%	75	5	420	1055
	F4	750	35%	37.5	5	450	1055
Methocel K 15M	F5	750	20%	150	5	400	1055
	F6	750	25%	112.5	5	420	1055
	F7	750	30%	75	5	450	1055
	F8	750	35%	37.5	5	480	1055
Methocel K 4M	F9	750	20%	150	5	400	1055
	F10	750	25%	112.5	5	440	1055
	F11	750	30%	75	5	420	1055
	F12	750	35%	37.5	5	490	1055
Ethocel 20 Prem	F13	750	20%	150	5	300	1055
	F14	750	25%	112.5	5	300	1055
	F15	750	30%	75	5	300	1055
	F16	750	35%	37.5	5	300	1055
Polyox WSR 300	F17	750	20%	150	5	350	1055
	F18	750	25%	112.5	5	400	1055
	F19	750	30%	75	5	440	1055
	F20	750	35%	37.5	5	310	1055

Procedure

- Weigh ingredients 1,2,3 and pass through 22 sieve
- Add ingredients 1 to ingredient 2 in RMG while dry mix followed by ingredient 3
- Granulate the above blend using water as per parameters specified
- The above granules are semi dried and are passed through cutter mill for breaking of lumps
- The above granules are dried to get required LOD

- Dried granules are passed through multi mill (cutter) and are passed through 20 sieve
- Thus obtained blend is lubricated with magnesium sterate (#60pass)
- The above blend is compressed using 21*10mm with specified parameters

Rapid Mixer Granulator (RMG)

- Rapid mixer granulator commonly called as RMG, which is used for the development of granules.
- It helps to determining how much amount of binder solution that we had to add.
- RMG is made up of stainless steel in which the bowel which is used for adding the ingredients will vary in size according to the batch we are using.
- Inside the bowel of RMG, there is chopper and impeller.
- The water (binder) which is added to the blend with the help of a lump (in which RPM is settled)
- The impeller will be rotating according to which RPM we setted, a continues action, it helps in the formation of granules.
- The chopper switch is on only when the big lumps are formed (to break the lump).
- Various parameters such as, time, impeller, chopper, amper reading is shown.
- It is good to operate the RMG in a closed position.

Fludised Bed Drier

- Flusided bed drier is also called as FBD apparatus.
- The size of the apparatus varies according to the batch size.
- The FBD apparatus mainly used for reducing the water content of the granules.
- Mainly we set the inlet temperature to 60°C.
- The various parameters shown here are time, inlet temperature, bed temperature, exhaust temperature inlet and exhaust relative humidity and percentage LOD.
- The operation is performed up to there is reduction in granules temperature less than 1.50%
- In drier apparatus, there is a blower (gun) which will allow the passage of air, as a result the granules will be uniformly scattered and flying inside the apparatus.

Sonic Swifter

- Sonic Swifter is mainly used for the particle size analysis.
- Here there are different measures arranged in a vertical position, i.e. the order from #16 to 80.
- These measures are arranged and packed properly.
- The sample (weighed) is added to the top i.e. #16 mesh.
- The vibrancy is used for 5 minutes.
- Larger granules will be in the topper serve and smaller granule will be in the bottom.
- The percentage returned is calculated by initial weight of sieve –wt after vibrating.

4.10. Evaluations of blend (granules)[45]

1. Sieve analysis.
2. Bulk density (g/ml).
3. Tapped density (g/ml).
4. Hausner ratio
5. Loss on drying.

1. Sieve analysis:

Take 100g of the dried un lubricated blend placed in the sieve shaker containing the mesh #20, #30, #40, #60, #80, #100, and #200. Shake the sieve by using electromagnetic sieve shaker for 5 min. Weight of empty mesh was noted and after shaking sieve the weight of mesh with granules was noted. Then % cumulative release was calculated to know the % retains of granules in each mesh.

2. Bulk density (g/ml):

Bulk density is the ratio between the mass of powder and its bulk volume. Apparent Bulk Density was determined by pouring the weighed granules into a graduated cylinder via. Funnel and measuring the volume. Density was calculated using the formula,

$$\text{Bulk Density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of powder}}$$

3. Tapped density (g/ml):

Tapped density is the ratio between a given mass of powder and its final volume after Tapping. It was determined by tapping a graduated cylinder containing a known mass of Granules for a fixed number of taps until the powder volume has reached minimum. The Tapped density was computed using the formula:

$$\text{Tapped Density} = \frac{\text{Mass of the powder}}{\text{Tapped Volume of the powder}}$$

4. Carr's Index (CI):

The flow ability of the granules was measured by the application of Compressibility

Carr's Index given by the equation:

$I = [1 - V/ V_o] .100$

Where,

V = Volume of the sample after tapping

V_o = Volume before tapping

Values of I:

- Below 15% give rise to good flow characteristics
- Above 25% indicate poor flow ability

Hausner's ratio:

It is measurement of frictional resistance of the drug. The ideal range should be 1.0-1.18. It is determined by the ratio of tapped density and bulk density

Hausner's ratio=Tapped density/Bulk density

Flow Properties

Table -8

Compressibility Index	**Flow character**	**Hauser ratio**
5-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.45
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
More than40	Very, Very poor	More than 1.60

5. Loss on drying:

Loss on drying was done using IR Moisture Analyzer to check the moisture content in the blend. The LOD should be below 3% for the blend. If it was on the higher side it will causes the sticking and picking.

Chemical and physical characterizations of drug substance are essential before the formulation development. Pre formulation studies give the information needed to define the nature of the drug substances and provide a framework for the drug combination with pharmaceutical Excipients in the fabrication of a dosage form

Analysis of Active Pharmaceutical Ingredient

The physicochemical characterization of active pharmaceutical ingredient like physical appearance, solubility, particle size analysis, identification test, alkalinity, loss on drying, impurity test and assay were performed.

Pre-formulation Study

Pre formulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre formulation study is to identify those physico-chemical properties and Excipients that may influence the formulation design, method of manufacture and pharmacokinetic and bio pharmaceutical properties of the product.

Pre formulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with Excipients under specified storage conditions.

4.11. Drug Excipients Compatibility Studies

Selection of Excipients:

The excipients which are being used in the reference product are selected. Apart from the excipients listed in the reference product, other excipients are also considered based on the possible use of them.

Method: The drug – excipients mixture was prepared in the duplicate ratio as mentioned in table number 9. The mixtures were filled into EP type I glass vials, sealed with rubber closures and aluminum caps, and subjected to accelerated condition

(6months in 40°C / 75 % RH), short term condition to check any physical changes and related substances level.

Table -9 Drug Excipients compatibility study table

S.No	Exceipients	40°C/75% Rh 6 months
1	Metformin	-
2	Metformin + Methocel K 100M	-
3	Metformin + Methocel K 15M	-
4	Metformin + Methocel K4M	-
5	Metformin + Ethocel 20Prem	-
6	Metformin + Polyox WSR 300	-
7	Metformin + Methocel K 100M + K15M + K4M+ Ethocel 20 Prem+ Polyox WSR 300	-

7. RESULTS AND DISCUSSION

Innovator results

Table -10

Metformin hydrochloride was subjected to the following tests and has passed all the tests for identification

Table -11

TESTS FOR METFORMIN HYDROCHLORIDE

Sl. No	Test	Limits as per monograph	Observation
1	Description	White crystals	Complies with USP
2	Solubility	Freely soluble in water , slightly soluble in alcohol , in soluble in acetone	Complies with USP
3	Melting point	122°C 125°C	123°C
4	Identification	IR absorption spectrum concordant with the reference spectrum	Complies with USP
5	Assay	95.0-98.0	

Table -12

TRIALS WITH DIFFERENT CONCENTRATION OF POLYMERS

1. WITH METHOCEL K100M

FORMULAT -ION CODE	METFORM IN	METHO CEL K100M AT DIFF CONC	MCC PH 101	Mg STER	Water (MI)	Total wt.
F1	750	150 (20%)	150	5	400	1055
F2	750	187.5 (25%)	112.5	5	400	1055
F3	750	225 (30%)	75	5	420	1055
F4	750	262.5(3	37.5	5	450	1055

Table -13

RMG PARAMETERS FOR F1

EX.NO :1 PUMP RPM:70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER QUANTITY	IMPELLER/ AMP	CHOPPER/ AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	100	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -14

RMG PARAMETERS OF F2

EX.NO:2 PUMP RPM:70			BOWEL CAPACITY.5lit		
TIME	STEP	BINDER QUANTITY	IMPELLER/ AMP	CHOPPER/ AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	100	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -15

RMG PARAMETERS OF F3

EXP.NO. 3 PUMP RPM - 40			BOWEL CAPACITY .5 lit		
TIME	STEP	BINDER QUANTITY	IMPELLER/ AMP	CHOPPER/ AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	PARTIAL WETTING OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	120	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -16

RMG PARAMETERS OF F4

EXP.NO: 4 PUMP RPM: 40			BOWEL CAPACITY .5 lit		
TIME	STEP	BINDER QUANTITY	IMPELLER/ AMP	CHOPPER/ AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	NO WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8		PARTIAL DIST
2:00	BINDER ADD	150	150/1.8	_	PARTIAL WETTING OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Discussion of RMG Parameters (F1-F4)

- According to all the parameters evaluation, the time consumption for all the formulation (F1….F4) is the same 38 minutes.
- Good granule were formed, the physical observation that inside the bowel, the flow of granule is like the water flow from a pipe.
- For F1 and F2 the binding consumption is same (400ml) and Four F3 and F4 the binder consumption vary from 420 and 450ml.
- Slight sticky to the side of the bowel observed.
- Big lumps formed, so frequent operation of chopper needed.

Table -17

FBD PARAMETERS OF F1

BATCH NO: 1 BLOWER SPEED 40Hz				SET TEMP 60°C			
TIME (MIN)	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	24	32	40	39	15.53	
10	59	24	33	42	35		RACKING
20	58	24	33	43	27		
30	57	43	35	70	31	6.53	
40	59	47	39	39	25	5.35	Bag suction
50	60	48	37	34	48	1.15	

Table -18

FBD PARAMETERS OF F2

BATCH NO: 2 BLOWER SPEED 40Hz				SET TEMP 60°C			
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	24	32	42	38	15.5	
10	58	24	33	43	36		racking
20	59	26	34	50	30		
30	59	41	35	52	41	5.89	
40	60	48	38	35	43	5.30	
50	60	49	39	36	49	1.30	

Table -19

FBD PARAMETERS OF F3

BATCH NO: 3 BLOWER SPEED 40Hz				SET TEMP 60°C			
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
10 0	58	25	35	40	36	16.25	
	52	26	39	39	38		
20	55	29	37	37	35		
30	59	35	40	36	41	10.10	
40	59	42	43	32	45	4.25	
50	60	53	45	31	52	1.3	

Table -20

FBD PARAMETERS OF F4

BATCH NO: 4 BLOWER SPEED 40Hz				SET TEMP 60°C			
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	49	21	34	45	36	16.25	
10	50	25	39	42	39		
20	53	30	41	36	35		Bag suction
30	55	35	43	34	41	10.10	
40	58	43	45	32	46	4.25	
50	60	50	49	31	53	1.30	

Discussion of FBD Parameter (F1-F4)

- The time consumed for the whole process is 50 minutes.
- The inlet temperature varies for all the formation varies from 58-60.
- All the formulation we got at 50 minutes the percentage LOD is less than 1.50
- Free flow of granules inside the apparatus.
- Uniform distribution of temperature for granules.

PARTICLE SIZE ANALYSIS

Table -21

For F 1

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.8	1.8 %
2	#16-18	8.9	10.7 %
3	#18-20	13.9	24.6 %
4	#20-30	18.5	43.1 %
5	#30-60	22.7	65.8 %
6	#60-80	25.8	91.6 %
7	#80 PASS	8.4	100 %

Table -22

FOR F2

SL.NO	SIEVE NO	% RET	COMM
1	#16	2.7	2.7%
2	#16-18	9.0	11.6%
3	#18-20	8.3	19.9%
4	#20-30	10.3	30.2%
5	#30-60	17.3	47.5%
6	#60-80	5.3	52.8%
7	#80 PAss	47.2	100%

Table -23

FOR F3

SL.NO	SIEVE NO	% RET	COMM
1	#16	3.5	2.8%
2	#16-18	9.3	11.8%
3	#18-20	9.6	19.7%
4	#20-30	10.2	30.4%
5	#30-60	17.9	47.7%
6	#60-80	5.2	52.7%
7	#80 PASs	47.9	100%

Table -24

FOR F4

SL.NO	SIEVE NO	% RET	COMM
1	#16	3.1	3.0%
2	#16-18	9.6	12.1%
3	#18-20	9.8	19.8%
4	#20-30	10.5	30.5%
5	#30-60	17.8	49.7%
6	#60-80	5.7	53.7%
7	#80 PASS	47.8	100%

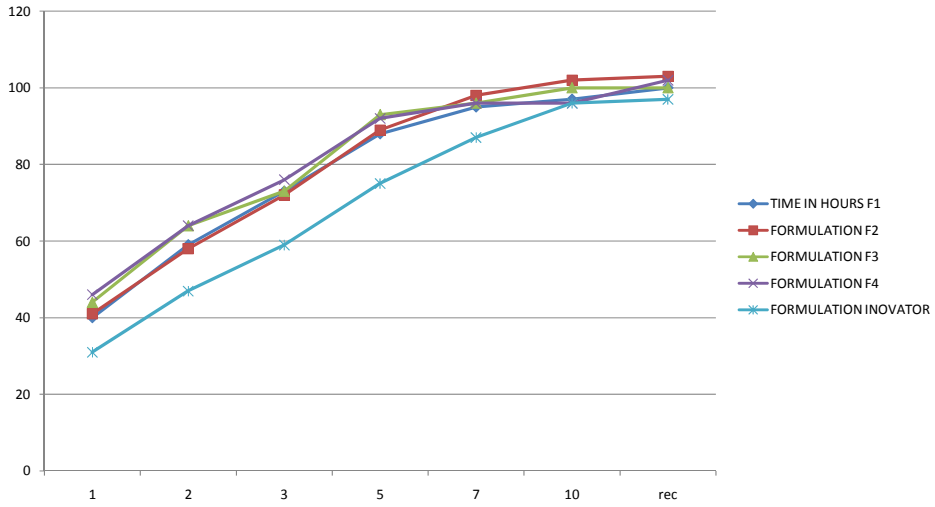
Table -25

COMPRESSION PARAMETERS

PUNCH SIZE	TABLET wt %	ACTUAL wt	TABLET THICK	TABLET HARDNESS	TURRET rpm	FRIABILITY	TD	BD	HR	FLOW
F1 21*10M	1055	1040-1060	5.39-5.43	15.96-16.30	6	0.58	0.52	0.42	1.23	FAIR-VIB
F2 21*10M	1055	1040-1060	5.40-5.45	15.98-16.35	6	0.58	0.51	0.43	1.18	GOOD-NOT ARC
F3 21#10M	1055	1037-1041	5.37-5.41	15.97-16.32	6	0.60	0.51	0.41	1.24	FAIR VIB
F4 21*10M	1055	1041-1047	5.36-5.39	15.60-15.97	6	0.59	0.62	0.53	1.16	GOOD NOT ARC

Table -26

Fig:9 Dissolution Graph of Methocel K100M



Discussion

- All the parameters thickness, hardness, friability were satisfactory as compared with innovator.
- But the dissolution is found to be varying as compared with innovator.
- For F1 – At the 1st and the 10th hour the release falls within the limit.3rd hour the release is so fast.
- For F2-- At the 1st and the 10th hour the release falls within the limit.3rd hour the release is so fast.
- For F3—1st hour the release is in border 3rd hour the Release is so fast.10th hour falls within the limit.
- For F4—1st and 3rd hour release is high.10th hour the release is satisfactory.

Table -27

2. WITH METHOCEL K15M

FORMULATION CODE	METFORMIN	METHO CEL K15 M	MCC PH 101	MG STER	H2O	TOTAL wt
F5	750	150 (20%)	150	5	400	1055
F6	750	187.5 (25%)	112.5	5	420	1055
F7	750	225 (30%)	75	5	450	1055
F8	750	262.5 (35%)	27.5	5	480	1055

Table -28

RMG PARAMETERS FOR F5

EX NO: 5 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	100	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -29

RMG PARAMETERS FOR F6

EX NO: 6 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	120	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB

Table -30

RMG PARAMETERS FOR F7

EX NO: 7 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	120	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
2:00 3;00	BINDER ADD KNEADING	30	150/1.8 200/1.8	_ 2250/0.7	- OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -31

RMG PARAMETERS FOR F8

EX NO: 8 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	 2250/0.7	 UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	120	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
2:00 3;00	BINDER ADD KNEADING	60	150/1.8 200/1.8	_ 2250/0.7	- OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Discussion on RMG Parameters (F5-F8)

- According to all the parameters evaluation, the time consumption for all the formulation (F5 to F8) as the same, i.e. 40 minutes.
- Good granules were formed, at 40 minutes, the blend just flow like a water flow from pipe.
- The binder consumption varies from F5-F8 i.e. 400-480ml.
- There is no sticking to the bowel.
- There is no lumps formation.
- Here there is frequent kneading required.
- The impeller parameter is frequently fluctuating.

Table -32

FBD PARAMETERS OF F5

BATCH NO: 5				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	55	26	32	34	44	15.37	
10	58	27	34	36	41		RACKING
20	60	33	34	38	30	11.21	
30	57	40	34	39	37	9.36	
40	60	36	32	38	35		
50	60	45	37	38	30	1.50	

Table -33

FBD PARAMETERS OF F6

BATCH NO: 6				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	54	23	29	31	39	15.37	
10	55	26	32	35	40		Bag suction
20	60	31	34	38	43	10.34	
30	57	38	35	38	38	5.54	
40	60	39	37	39	36		
50	60	40	38	39	32	1.34	

Table -34

FBD PARAMETERS OF F7

BATCH NO: 7				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	56	29	33	35	45	12.67	
10	57	30	35	38	42		
20	59	28	37	39	30	9.65	RACKING
30	58	32	36	42	35	4.89	Bag suction
40	59	35	38	39	36		
50	60	37	40	38	30	1.20	

Table -35

FBD PARAMETERS OF F8

BATCH NO: 8				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	25	35	40	36	16.25	
10	52	26	39	39	38		Racking
20	55	29	37	37	35		
30	59	35	40	36	41	10.10	
40	59	42	43	32	45	4.25	
50	60	53	45	31	52	1.3	

Discussion on FBD Parameters (F5-F8)

- Here the blower speed set for 40Hz.
- The inlet temperature is set for 60°C
- The time consumed for the whole process is 50 minutes.
- The inlet temperature 56-60.
- The bed temperature ranges from 23-45.
- All the formulation we got at 50 minutes the percentage LOD is less than 1.50.
- Free flow of granules inside the apparatus.
- Bag suction is frequently needed.
- Temperature is uniformly distributed to granules.

Table -36

PARTICLE SIZE ANALYSIS FOR F5

SL.NO	SIEVE NO	% RET	CUMULATIVE RELEASE
1	#16	1.0	1.0
2	#16-18	8.9	9.9
3	#18-20	9.2	19.1
4	#20-30	13.9	33.0
5	#30-60	26.4	59.0
6	#60-80	6.9	66.3
7	#80 PASS	33.7	100%

Table -37

PARTICLE SIZE ANALYSIS FOR F6

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.3	1.3 %
2	#16-18	3.1	4.4 %
3	#18-20	9.7	14.1 %
4	#20-30	15.7	29.8 %
5	#30-60	23.7	53.5 %
6	#60-80	16.6	70.1 %
7	#80 PASS	31.6	100 %

Table -38

PARTICLE SIZE ANALYSIS FOR F7

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.7	1.7 %
2	#16-18	5.9	7.6 %
3	#18-20	12.5	20.1 %
4	#20-30	16.5	36.6 %
5	#30-60	24.6	61.2 %
6	#60-80	20.3	81.5 %
7	#80 PASS	30.5	100 %

Table -39

PARTICLE SIZE ANALYSIS FOR F8

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	2.1	2.1 %
2	#16-18	8.1	10.2 %
3	#18-20	12.8	23 %
4	#20-30	19.6	42.6 %
5	#30-60	25.7	68.3 %
6	#60-80	20.7	89 %
7	#80 PASS	33.6	100 %

Table -40

COMPRESSION PARAMETERS

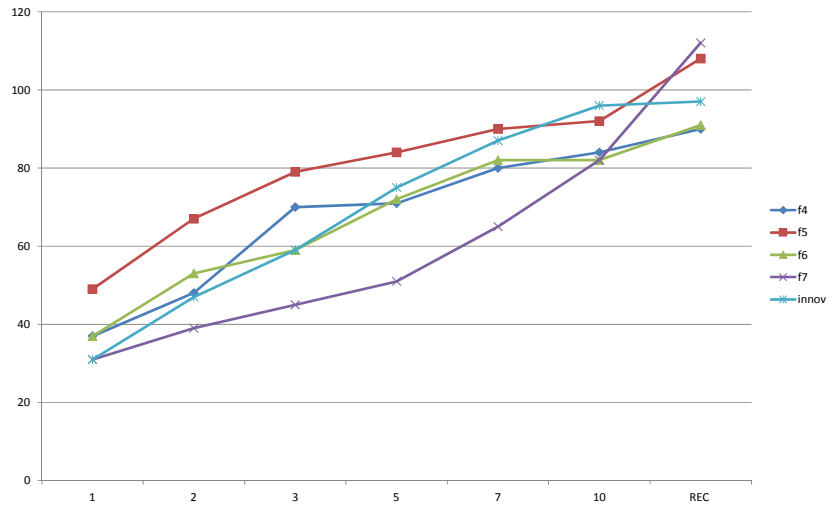
PUNCH SIZE	TABLET wt %	ACTUAL wt	TABLET THICK	TABLET HARDNESS	TARRET rpm	FRIABILITY	TD	BD	HR	FLOW
F5 2 1*10M	1055	1040-1066	5.10-5.30	14.39-16.10	6	0.60	0.50	O.42	1.19	FAIR VIB
F6 21*10M	1055	1043-1061	5.15-5.40	14.30-16.20	6	0.63	0.51	0.42	1.21	FAIR VIB
F7 21#10M	1055	1040-1060	5.20-5.50	14.00-16.20	6	0.62	0.52	0.42	1.23	FAIR VIB
F8 21*10M	1055	1045-1065	5.13	14.35-16.30	6	0.67	0.61	0.52	1.71	GOOD NOT ARC

Table -41

DISSOLUTION DATA

TIME IN HOURS	FORMULATIONS			
	F5	F6	F7	F8
1	37	49	37	31 .....
2	48	67	53	39
3	70	79	70 =	51 .....
5	71	84	72	51
7	80	90	82	65
10	84	92	82	82
REC	90	108	91	112
Assay	98	98	99	99

Fig:10 Dissolution Graph of Methocel K15M



Discussion

- For F5—1st hour and the 10th hour the release is satisfactory.3rd hour the release is slightly high.
- For F6– 1st and the 3rd hour is high.10th hour the release is up to limit.
- For F7– 1st and 3rd hour the release is moderate.10th hour the release is very slow that is less than 85%.
- For F8 – 1st and 3rd hour the release is moderate.10th hour the release is very slow.

Table -42

3.WITH METHOCEL K4M

FORM CODE	METFORM	METHOCEL K4M	MCC PH 101	MG STER	WATER	TOTAL wt
F9	750	150 (20%)	150	5	400	1055
F10	750	187.5 (25%)	112.2	5	440	1055
F11	750	225 (30%)	75	5	420	1055
F12	750	262.5 (35%)	37.5	5	490	1055

Table -43

RMG PARAMETERS FOR F9

EX NO: PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	100	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -44

RMG PARAMETERS FOR F10

EX NO: 10 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	**STEP**	**BINDER ADDITION**	**IMPELLER SPEED/AMP**	**CHOPPER SPEED/AMP**	**OBSERVATION**
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	140	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
3;00	KNEADING		200/1.8	2250/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -45

RMG PARAMETERS FOR F11

EX NO: 11 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	**STEP**	**BINDER ADDITION**	**IMPELLER SPEED/AMP**	**CHOPPER SPEED/AMP**	**OBSERVATION**
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	120	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
2:00 3;00	BINDER ADD KNEADING	30	150/1.8 200/1.8	_ 2250/0.7	- OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -46

RMG PARAMETERS FOR F12

EX NO: 12 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	**STEP**	**BINDER ADDITION**	**IMPELLER SPEED/AMP**	**CHOPPER SPEED/AMP**	**OBSERVATION**
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	 2250/0.7	 UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	120	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
2:00 3;00	BINDER ADD KNEADING	60	150/1.8 200/1.8	_ 2250/0.7	- OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Discussion on RMG Parameters for F9 to F12

- According to all the parameters evaluation the time consumption for all the formulation (F9-F12) is not uniform.
- For F9 & F10 it is 38 minutes and F11 & F12 it is 40 minutes.
- Good granules were formed.
- The binder consumption varies from 400 to 490ml.
- Big lumps formed, chopper operation needed.
- Especially for F11 the kneading time increases.

Table -47

FBD PARAMETERS OF F9

BATCH NO: 9 BLOWER SPEED 40Hz				SET TEMP 60°C			
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	24	32	42	38	15.5	
10	58	24	33	43	36		racking
20	59	26	34	50	30		
30	59	41	35	52	41	5.89	
40	60	48	38	35	43	5.30	
50	60	49	39	36	49	1.30	

Table -48

FBD PARAMETERS OF F10

BATCH NO: 10				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
10	58	25	35	40	36	16.25	
0	52	26	39	39	38		
20	55	29	37	37	35		
30	59	35	40	36	41	10.10	Bag suction
40	59	42	43	32	45	4.25	
50	60	53	45	31	52	1.3	

Table -49

FBD PARAMETERS OF F11

BATCH NO: 11 BLOWER SPEED 40Hz				SET TEMP 60°C			
TIME (MIN)	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	24	32	40	39	15.53	
10	59	24	33	42	35		RACKING
20	58	24	33	43	27		
30	57	43	35	70	31	6.53	
40	59	47	39	39	25	5.35	
50	60	48	37	34	48	1.15	

Table -50

FBD PARAMETERS OF F12

BATCH NO: 12				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
10	58	25	35	40	36	16.25	
0	52	26	39	39	38		RACKING
20	55	29	37	37	35		
30	59	35	40	36	41	10.10	
40	59	42	43	32	45	4.25	
50	60	53	45	31	52	1.3	

Discussion on FBD Parameters

- Blower speed is 40 Hz.
- Inlet temperature 60°C.
- Inlet temperature varies from 58 to 60 and of bed temperature is from 24 to 48.
- The time consumption for whole process is 50minutes.
- The percentage of LOD we got within 50minutes is less than 1.50.
- Here we observed that the granules settled at the bottom.
- The granules were so hard.

Table -51

PARTICLE SIZE ANALYSIS FOR F9

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.4	1.4 %
2	#16-18	6.3	7.7 %
3	#18-20	11.3	19 %
4	#20-30	17.8	36.7 %
5	#30-60	21.5	58.3 %
6	#60-80	16.7	75 %
7	#80 PASS	32.6	100 %

Table -52

PARTICLE SIZE ANALYSIS FOR F10

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.7	1.7 %
2	#16-18	5.2	6.9 %
3	#18-20	12.5	19.4 %
4	#20-30	16.2	35.6 %
5	#30-60	21.5	57.1 %
6	#60-80	16.8	73.9 %
7	#80 PASS	26.1	100 %

Table -53

PARTICLE SIZE ANALYSIS FOR F11

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.2	1.2 %
2	#16-18	6.2	7.4 %
3	#18-20	10.5	17.9 %
4	#20-30	15.8	33.7 %
5	#30-60	21.4	55.1 %
6	#60-80	25.7	80.8 %
7	#80 PASS	19.2	100 %

Table -54

PARTICLE SIZE ANALYSIS FOR F12

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.4	1.4 %
2	#16-18	5.9	7.3 %
3	#18-20	11.2	18.3 %
4	#20-30	18.9	37.7 %
5	#30-60	25.7	63.3 %
6	#60-80	16.9	80.3 %
7	#80 PASS	19.7	100 %

Table -55

COMPRESION PARAMATER

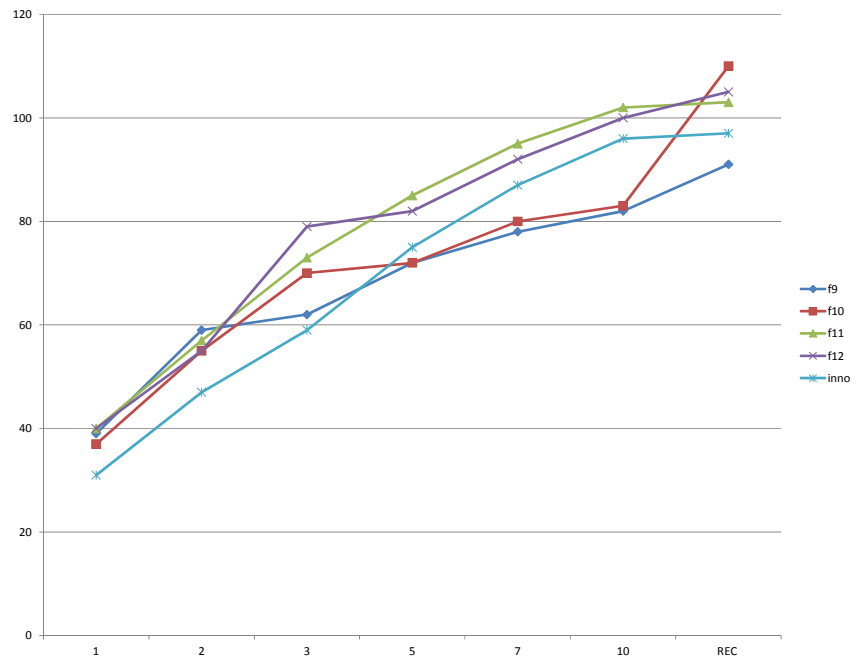
PUNCH SIZE	TABLET wt %	ACTUAL wt	TABLET THICK	TABLET HARDNESS	TARRET rpm	FRIABILITY	TD	BD	HR	FLOW
F9 21*10M	1055	1020-1059	5.30-5.90 MM	12.8-13.6	6	0.56	0.60	0.49	1.22	FAIR VIB
F10 21*10M	1055	1022-1058	5.30-5.90	12.8-13.9	6	0.63	0.51	0.41	1.24	FAIR VIB
F11 21#10M	1055	1020-1060	5.30-5.90	12.9-13.7	6	0.69	0.50	0.42	1.21	FAIR VIB
F12 21*10M	1055	1030-1065	5.31-5.94	12.90-14.24	6	0.68	0.52	0.43	1.20	FAIR VIB

Table -56

DISSOLUTION DATA

TIME IN HOURS	FORMULATIONS			
	F9	F10	F11	F12
1	39	37	40	40 .....
2	59	55	57	55
3	62	70 =	73	79
5	72	72	85	82
7	8O	80	95	92
10	82	83	102	100 .....
REC	91	110	103	105
Assay	99	99	98	98

Fig:11 Dissolution Graph of Methocel K4M



Discussion

- For F9—1st and third hour the release is moderate.10th hour the release is very slow.
- For F10—1st and 3rd hour the release is moderate and 10th hour the release is very slow.
- For F11—1st and 10 hour the release is moderate but 3rd hour the release increases.
- For F12-- F11—1st and 10 hour the release is moderate but 3rd hour the release increases
- The granules are so hard.
- So we go for multi mill apparatus.

Table -57

4. WITH ETHOCEL 20 PREM

FORMULATION	MET	ETHOCEL 20 PRE	MCC PH 101	MG STER	WATER	TOTAL wt
F13	750	150 (20%)	150	5	300	1055
F14	750	187.5 (25%)	112.5	5	300	1055
F15	750	225 (30%)	75	5	300	1055
F16	750	262.5 (35%)	37.5	5	300	1055

Table -58

RMG PARAMETERS FOR F13

EX NO: 13 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	OPT GRANU OBTAINED
2:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -59

RMG PARAMETERS FOR F14

EX NO: 14 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	OPT GRANU OBTAINED
2:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -60

RMG PARAMETERS FOR F15

EX NO: 15 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	OPT GRANU OBTAINED
2:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -61

RMG PARAMETERS FOR F16

EX NO: 16 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	150	150/1.8	_	OPT GRANU OBTAINED
2:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Discussion on RMG Parameters for F13to F16

- According to all the parameters evaluation, the time consumption for all the formulation is very less only 21minutes.
- Granules were formed, but it is not uniform granules.
- The binder consumption is very less as 300ml.
- At all the concentration with 300ml of water good granules were formed.
- There is a not big lump.
- Uniform kneading time required.

Table -62

FBD PARAMETERS OF F13

BATCH NO: 13				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	29	31	29	41	15.69	
10	58	30	33	33	38		RACKING
20	61	33	33	35	36	8.32	
30	65	35	35	36	37	3.54	
40	68	42	36	37	35		
50	59	45	37	38	30	1.50	

Table -63

FBD PARAMETERS OF F14

BATCH NO: 14				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	57	29	31	30	42	16.54	
10	57	32	33	33	37		RACKING
20	61	33	34	34	36	10.24	
30	65	37	37	36	38	5.65	
40	68	42	36	39	35		
50	60	45	37	38	31	1.50	

Table -64

FBD PARAMETERS OF F15

BATCH NO: 15				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	55	25	31	32	42	14.98	
10	57	35	31	33	35		RACKING
20	63	33	34	34	36	11.24	
30	65	38	39	35	36	4.35	
40	67	42	39	39	35		
50	60	44	39	38	31	1.30	

Table -65

FBD PARAMETERS OF F16

BATCH NO: 16				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	58	25	33	31	45	13.24	
10	56	35	31	32	35		RACKING
20	62	33	37	34	36	10.12	
30	65	38	39	36	37	3.24	
40	67	42	39	38	35		
50	59	44	39	38	33	1.45	

Discussion on FBD parameters for F13-F16

- Blower speed is same i.e. 40Hz.
- Inlet temperature 60°C.
- Inlet temperature varies to 57-60°C and bed temperature from 29-45°C.
- The percentage LOD is less than 1.50 within 50 minutes.
- Frequency suction of bag needed.
- Sticking to side of wall occurs.

Table -66

PARTICLE SIZE ANALYSIS FOR F13

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.3	1.3
2	#16-18	6.8	8.1
3	#18-20	11.3	19.4
4	#20-30	19.6	39
5	#30-60	21.4	60.4
6	#60-80	16.8	77.2
7	#80 PASS	22.8	100

Table -67

PARTICLE SIZE ANALYSIS FOR F14

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.7	1.7 %
2	#16-18	5.2	6.9 %
3	#18-20	10.3	17.2 %
4	#20-30	12.6	29.8 %
5	#30-60	16.6	46.4 %
6	#60-80	20.5	66.9 %
7	#80 PASS	33.7	100 %

Table -68

PARTICLE SIZE ANALYSIS FOR F15

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.8	1.8 %
2	#16-18	8.9	10.7 %
3	#18-20	13.9	24.6 %
4	#20-30	18.5	43.1 %
5	#30-60	22.7	65.8 %
6	#60-80	25.8	91.6 %
7	#80 PASS	8.4	100 %

Table -69

PARTICLE SIZE ANALYSIS FOR F16

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.1	1.1 %
2	#16-18	4.7	5.8 %
3	#18-20	10.7	16.5 %
4	#20-30	13.7	30.2 %
5	#30-60	16.2	46.4 %
6	#60-80	15.7	62.1 %
7	#80 PASS	37.9	100 %

Table -70

COMPRESSION PARAMETERS

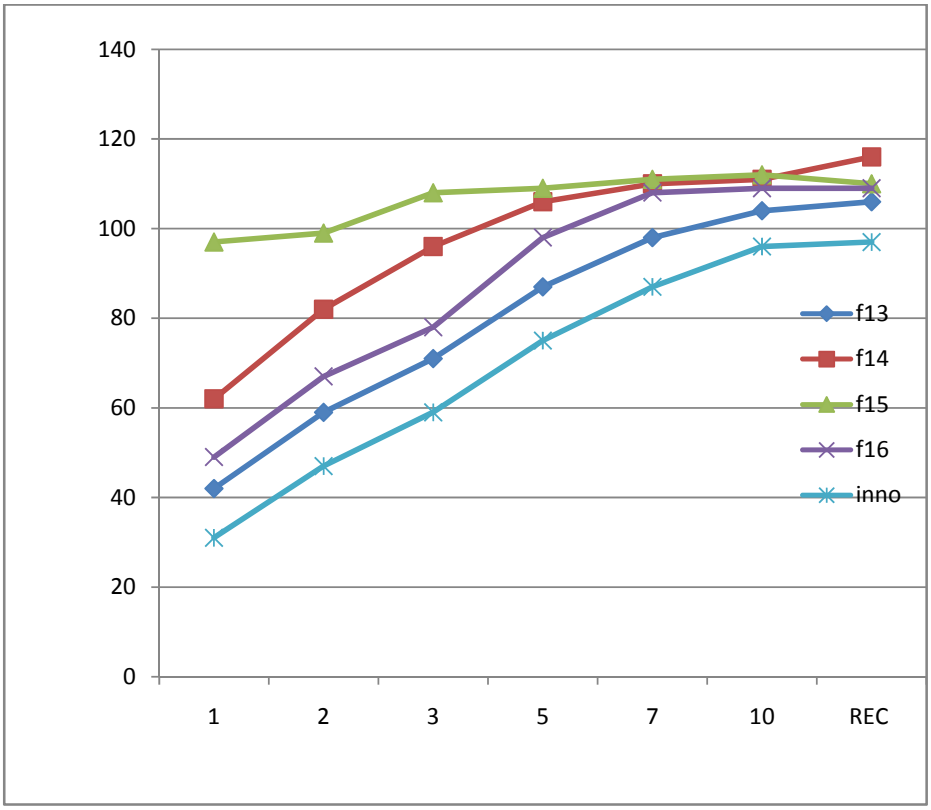
PUNCH SIZE	TABLET wt %	ACTUAL wt	TABLET THICK	TABLET HARDNESS	TARRET rpm	FRIABILITY	TD	BD	HR	FLOW
F13 2 1*10M	1055	1030-1062	5.10-5.30	15.25-16.00	6	0.53	0.61	0.41	1.48	VERY POOR AGIT
F14 21*10 M	1055	1032-1045	5.73-5.41	15.85-16.39	6	0.59	0.62	0.46	1.34	BORD PASS MAT HANG UP
F15 21#10 M	1055	1040-1061	5.50-5.65	15.98-16.34	6	0.42	0.60	0.44	1.36	POOR MASS AGIT
F16 21*10 M	1055	1049-1057	5.67-5.96	15.65-15.43	6	0.45	0.60	0.48	1.24	FAIR VIB

Table -71

DISSOLUTION DATA

TIME IN HOURS	FORMULATIONS			
	F13	F14	F15	F16
1	42 ….	62	97	49
2	59	82	99	67
3	71	96	108	78
5	87	106	109	98
7	98	110	111	108
10	104 …..	111 …..	112 ……	109 ……
REC	106	116	110	109
Assay	99	99	98	99

Fig:12 Dissolution Graph of Ethocel 20 Premium



Discussion

- In F13 to F16 the release is very slow at 1st and 3rd hour and 10th hour the release is moderate.
- Only in case of F13 the release is satisfactory with 1st and 10th hour.

Table -72

5.WITH POLYOX WSR 300

FORM CODE	METFORM	METHOCEL K4M	MCC PH 101	MG STER	WATER	TOTAL wt
F17	750	150 (20%)	150	5	350	1055
F18	750	187.5 (25%)	112.5	5	400	1055
F19	750	225 (30%)	75	5	440	1055
F20	750	262.5 (35%)	37.5	5	310	1055

Table -73

RMG PARAMETERS FOR F17

EX NO: 17 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	100	150/1.8	_	VERY SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	100	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -74

RMG PARAMETERS FOR F18

EX NO: 18 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00	KNEADING	_	200/1.8	2250/0.7	UNI DIST
2:00	BINDER ADD	100	150/1.8	_	VERY SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	_
5:00	KNEADING	_	200/1.8	2880/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -75

RMG PARAMETERS FOR F19

EX NO: 19 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
TIME (HH:MM)	STEP	BINDER ADDITION	IMPELLER SPEED/AMP	CHOPPER SPEED/AMP	OBSERVATION
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	140	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
3;00	KNEADING		200/1.8	2250/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Table -76

RMG PARAMETERS FOR F20

EX NO: 20 PUMP RPM : 70 rpm			BOWEL CAPACITY .5 lit		
(HH:MM)		ADDITION	SPEED/AMP	SPEED/AMP	
10:00	DRY MIX	_	200/1.8-1.9	_	UNI MIX
2:00	BINDER ADD	150	150/1.8	_	PAR WET OF BL
2:00	KNEADING	_	200/1.8	_	
3:00 2:00	KN EADING KNEADING	_ -	200/1.8 200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	150	150/1.8	_	SLIGHT WETT OF BLEN
2:00	KNEADING	_	200/1.8	_	_
3:00	KNEADING		200/1.8	2250/0.7	UNI DIS
2:00	BINDER ADD	160	150/1.8	_	_
2:00	KNEADING	_	200/1.8	_	NOT OPT GRAULES
3;00	KNEADING		200/1.8	2250/0.7	OPT GRNU OB
5:00	KNEADING	_	200/1.8	2880/0.7	SLI OVER GRA

Discussion on RMG Parameters F17to F20

- According to all the parameters evaluated the time consumption for all the formulation (F17-F20) is the same 38 minutes.
- Good granules, formed
- Uniform size granules
- The physical observation that inside the bower, the flow of granules is like the water flow from a pin.
- The binder consumption varies from 350-440ml.
- No big lump formed.
- Uniform kneading required.

Table -77

FBD PARAMETERS OF F17

BATCH NO: 17				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	55	22	31	40	39	14.32	
10	56	24	33	42	35		
20	58	43	35	43	27		RACKING
30	57	47	38	70	31	5.63	
40	59	48	39	39	25	3.32	
50	60	49	37	34	48	1.15	

Table -78

FBD PARAMETERS OF F18

BATCH NO: 18				SET INLET TEMP 60°C			
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	40	20	31	43	39	12.12	
10	42	24	36	42	35		
20	49	30	35	43	27		RACKING
30	52	35	39	34	31	8.97	
40	56	41	39	39	25	4.56	Bag suction
50	60	49	37	34	48	1.15	

Table -79

FBD PARAMETERS OF F19

BATCH NO: 19			SET INLET TEMP 60°C				
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	54	22	36	40	35	15.15	RACKING
10	55	24	33	42	35		
20	58	43	35	46	27		
30	56	47	38	49	38	10.32	
40	56	48	39	49	25	5.76	
50	60	49	37	34	48	1.15	

Table -80

FBD PARAMETERS OF F20

BATCH NO: 20			SET INLET TEMP 60°C				
BLOWER SPEED 40Hz							
TIME	TEMPERATURE			RELATIVE HUMIDITY		% LOD	REMARK
	INLET	BED	EXHAUST	INLET	EXHAUST		
0	50	20	36	48	35	13.76	RACKING
10	52	24	37	46	33		
20	58	37	38	49	28		
30	56	47	38	49	38	11.67	
40	56	44	38	36	28	6.73	
50	60	49	39	34	48	1.15	

Discussion of FBD Parameters F17 to F20

- Time consumption for the whole process if 50 minutes.
- The inlet temperature varies from 40-60°C and bed temperature varies from 20-48°C.
- Free flow of granules inside the apparatus
- Uniform distribution of temperature in granules
- The percentage LOD is less than 1.50.

Table -81

PARTICLE SIZE ANALYSIS FOR F17

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.3	1.3 %
2	#16-18	4.4	5.7 %
3	#18-20	8.9	14.6 %
4	#20-30	12.6	27.2 %
5	#30-60	17.5	44.2 %
6	#60-80	21.3	66n %
7	#80 PASS	22.6	100 %

Table -82

PARTICLE SIZE ANALYSIS FOR F18

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.4	1.4 %
2	#16-18	4.5	5.9 %
3	#18-20	6.8	12.7 %
4	#20-30	12.5	25.2 %
5	#30-60	17.8	43 %
6	#60-80	21.6	64.6 %
7	#80 PASS	35.4	100 %

Table -83

PARTICLE SIZE ANALYSIS FOR F19

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.5	1.5 %
2	#16-18	6.1	7.6 %
3	#18-20	8	15.6 %
4	#20-30	13.1	28.7 %
5	#30-60	16.7	45.4 %
6	#60-80	20.3	65.7 %
7	#80 PASS	34.3	100 %

Table -84

PARTICLE SIZE ANALYSIS FOR F20

SL.NO	SIEVE NO	% RET	CUMULATIVE FREQUENCY
1	#16	1.8	1.8 %
2	#16-18	6.5	8.3 %
3	#18-20	10.3	18.6 %
4	#20-30	13.5	32.1%
5	#30-60	16.9	49 %
6	#60-80	21.4	70.4 %
7	#80 PASS	29.6	100 %

Table -85

COMPRESSION PARAMETERS

PUNCH SIZE	TABLET wt %	ACTUAL wt	TABLET THICK	TABLET HARDNESS	TARRET rpm	FRIABILITY	TD	BD	HR	FLOW
F17 2 1*10M	1055	1074.17 - 1075.63	6.54-6.95	12.9-13.7	6	0.69	0.53	0.46	1.15	GOOD NOT ARC
F18 21*10 M	1055	1076.78 - 1077.85	6.32-6.76	12.69-12.99	6	0.67	0.61	0.52	1.17	GOOD NOT ARC
F19 21#10 M	1055	1081.23 - 1084.67	7.01-7.93	13.58-14.1	6	0.58	O.62	0.53	1.16	GOOD NOT ARC
F20 21*10 M	1055	1086.32 - 1089.46	6.81-6.93	14.30-16.20	6	0.55	0.60	O.51	1.20	GOOD NOT

Table -86

DISSOLUTION DATA

TIME IN HOURS	FORMULATIONS			
	F17	F18	F19	F20
1	32	33 ------	39	38 .....
2	39	53	55	49
3	59	64 --------	67	69 .....
5	67	8O -------	82	83
7	75	88 ------	92	92
10	90	94 -------	98	105 .....
REC	100	96	104	104
Assay	98	98	99	99

Fig:13 Dissolution Graph of Polyox WSR 300

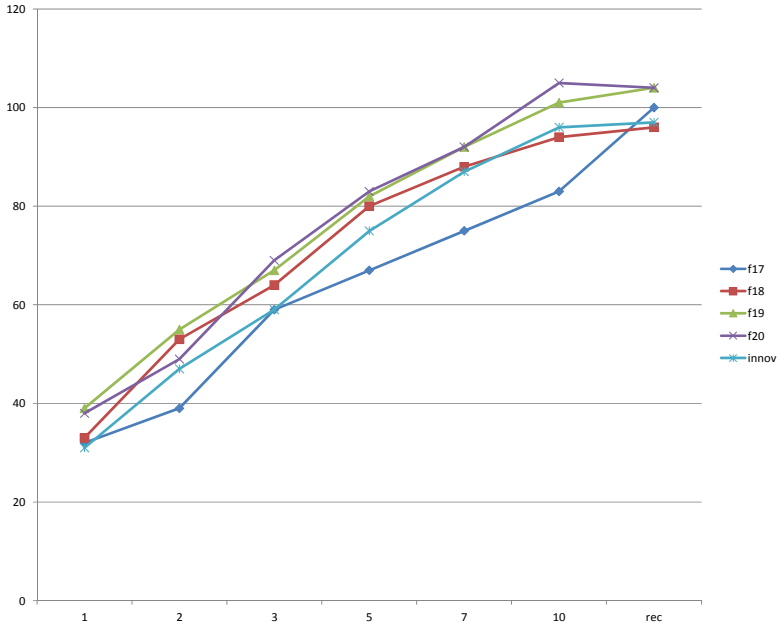


Fig:14 Standard assay

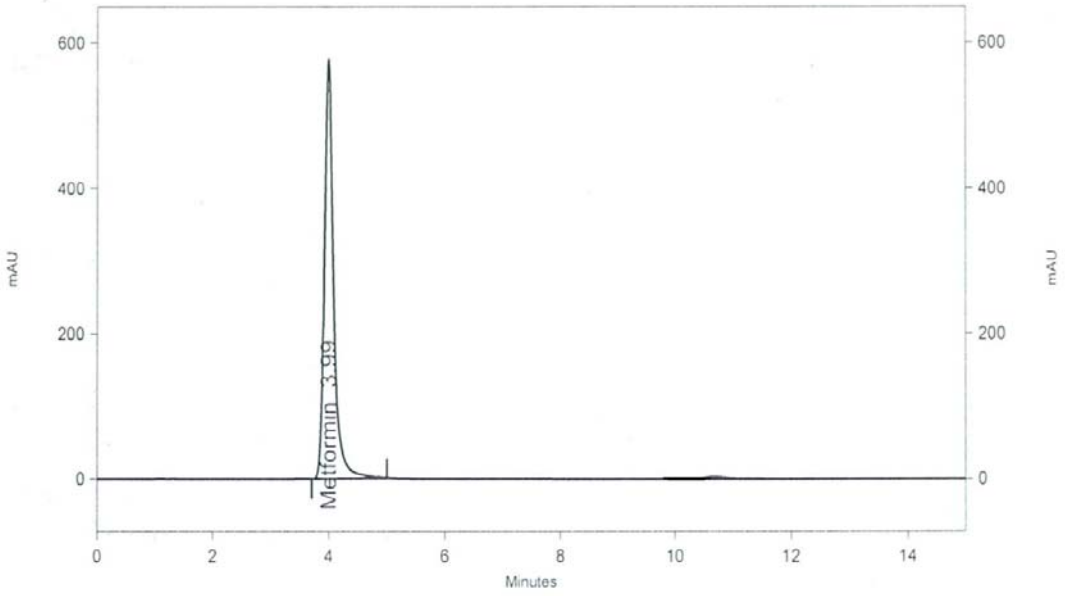


Fig:15 Sample of Assay

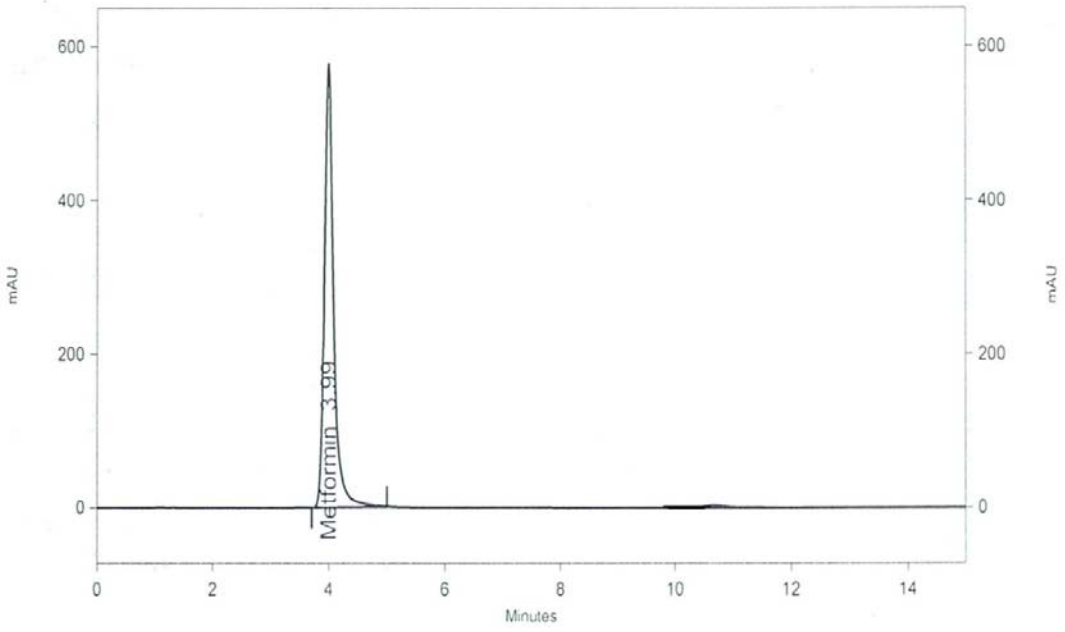


Fig:16 Standard for Dissolution

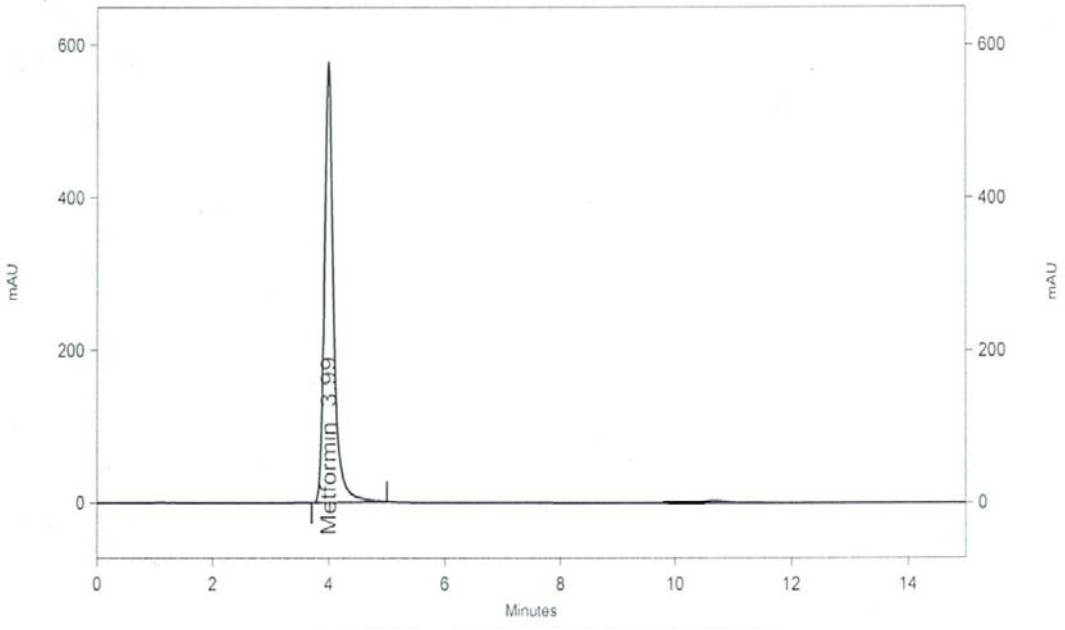


Fig:17 1st HOUR OF DISSOLUTION

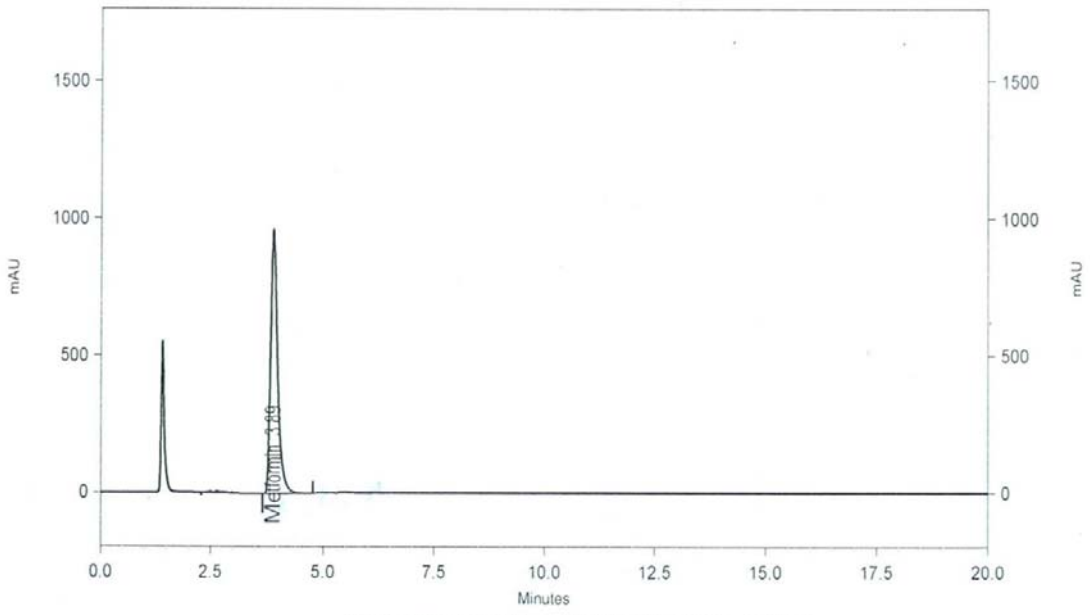


Fig:18 3rd HOUR OF DISSOLUTION

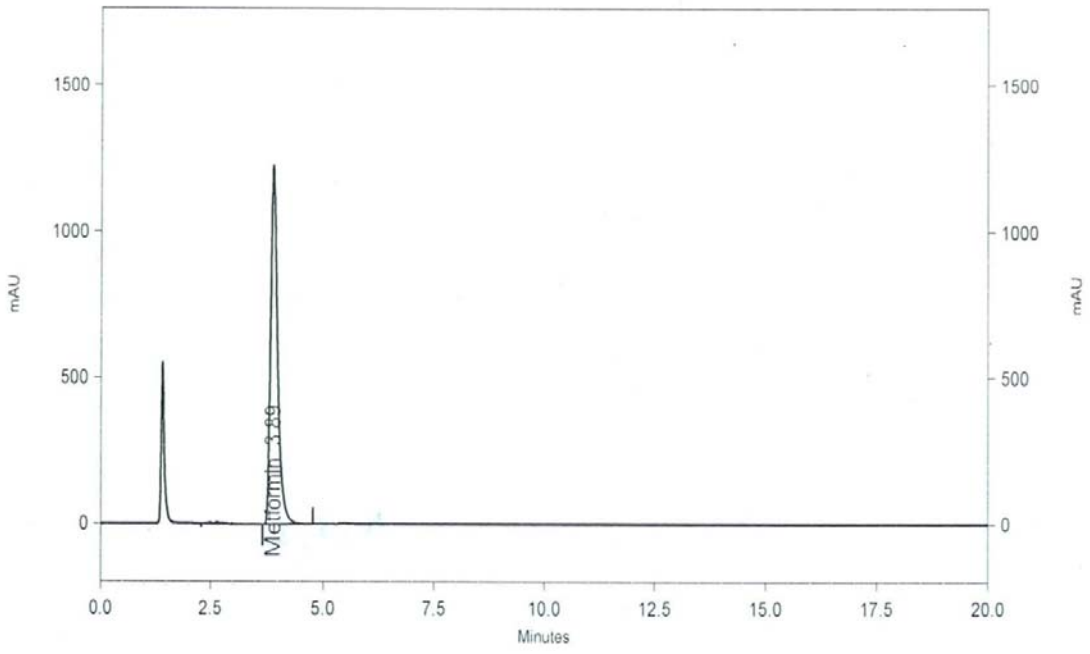
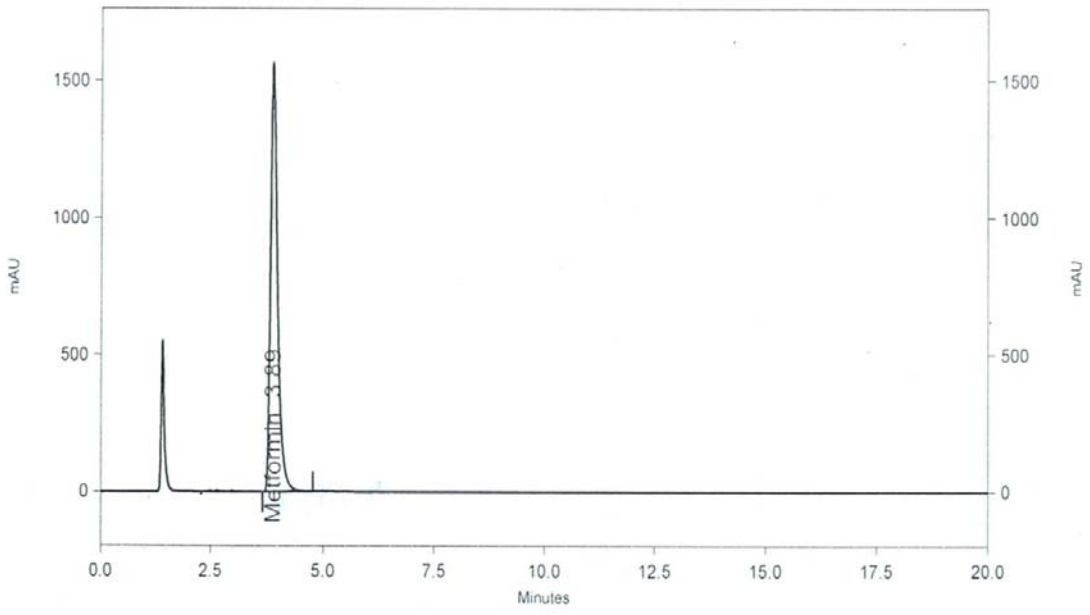


Fig:19 10th HOUR OF DISSOLUTION



Discussion

- All the formulations show the satisfactory release but the release is not steady.
- For dissolution and assay by HPLC method it is identified that for assay we get for F19 is 99 percentage and for Dissolution we got the percentage release 98 percentage.

Stability Study of F19

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products various with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for the drug distance or a shelf life for the drug product and recommended storage condition. Hence the tablets were loaded at accelerated condition at 40°C/75%RH (short term). Samples were withdrawn at an initial , 1st 2nd 6th month , and evaluated for colour hardness and drug release.

Table -87

Formulation F19 Stability Study Data

S.No	Parameters	F19			
		1st month	**2nd month**	**3rd month**	**6th month**
1	Colour	White	White	White	white
2	Hardness	4-6	4-6	4-6	3.9
3	Drug content (%)	99	99	98.9	98.1
4	% cumulative release	98.90	98.88	98.68	98.10

Table -88

Glucophage XR

S.No	Parameters	GLUCOHAGE XR 750 mg			
		1st month	**2nd month**	**3rd momth**	**6th month**
1	Colour	White	White	White	white
2	Hardness	12.7	12.7	12.5	12
3	Drug content (%)	97.8	97.5	96.6	96.1
4	% cumulative release	98.97	98.30	98.14	98.9

8. SUMMARY AND CONCLUSION

The present work was aimed at formulation and evaluation of sustained release metformin hydrochloride matrix tablets(750mg) with five different polymers and 4 different concentration 20%, 25%, 30%, 35% to find out which polymer is giving a best sustain release.

Pre formulation Study

The blends for formulating tablets were prepared according to the formulation scheme. The pre formulation study like bulk density, tapped density, angle of repose, Hausners ratio were done. The results obtained were within the acceptable limit and showing good flow property.

Compatibility Study

Compatibility study of metformin hydrochloride and metformin with different polymers like Methocel K100M, Methocel K4M, Methocel K15M, Ethocel 20 premium, Polyox WSR 300 at short term conditions(40/75%RH) for six months were evaluated, there is no cake formation, liquid formation or big lumps.

Formulation

The tablets were prepared by wet granulation method and punched with the help of 10 station punching machine of 19 x 21mm punch, to attain a target weight of 1050mg. the prepared tablets were evaluated for their post compression parameters like diameter, thickness, hardness, friability and weight variation test. The results obtained were within the acceptable limit.

Evaluation of Tablets

The compressed tablets were than evaluated for various test like hardness, weight variation, content uniformity, friability, etc as per the method given in USP, all the 20 formulation passed in the test with values with the limit prescribed by the USP.

Invitro Dissolution Study

- Mainly done in HPLC method
- The invitro dissolution studies showing that all the formulation gives a sustained release but it is not matching with the innovator.

- Only the F17, F18, F19, F20 matches with the innovated.
- The study showed that these polymers can be effectively used as matrix material for the preparation of sustained release matrix tables of metformin.

Stability Study

The chosen best formulation were kept for stability study as per ICH guideline in a stability chamber for a period of six month (short term) and parameters like physical appearance, weight variation, hardness, drug content and dissolution rate were studied at the end of 1^{st} 2^{nd} 3^{rd} and 6^{th} month. Study has a long shelf life.

RMG Parameters

- All the 20 formulations we had performed granulation with the help of RMG apparatus.
- All the formulations has given good granules
- According to the batch size vary in time
- The binder consumption also varies.
- In F19 the parameters are moderate and the granules formed are good.

FBD Parameters

- All the formulation are subjected to FBD apparatus.
- In F19 formulation we get the percentage LOD less than 1.20 in 30 minutes.
- The bag dumping is needed only at 25 minutes.
- So F19 formulation it is easy to handling in FBD apparatus.

Particle size analysis

- As compressed to all formulation, the F19 had a particle size of comparable range.
- It is detected in sonic swifter.
- In F19 we got in the range of 100%.
- As compared with Tapped density and Bulk density. The Hauser's ratio we got in the range of 1.16, the protocols states that, have a good flow, there won't be arc formation.

CONCLUSION

From the study, it may be concluded that F19 is the best formulation and can be manufactured with reproducible characteristics from batch to batch to match the release profile with innovator product. The findings of the present study ensure the company (Suven Nishtaa Pharma Pvt Ltd, Pashamylaram, Patancheru Mandal, Medak Dist, Andhra Pradesh) to launch the product in the market in near feature.

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